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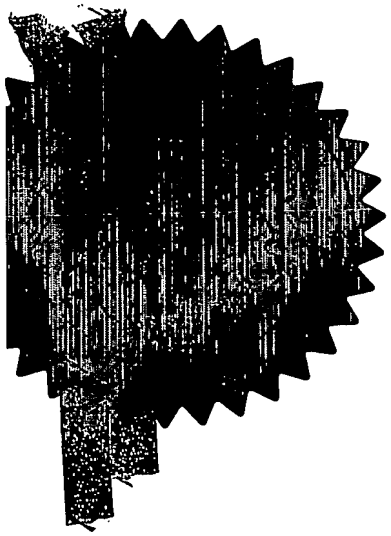

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Request for grant of a patent

1/77

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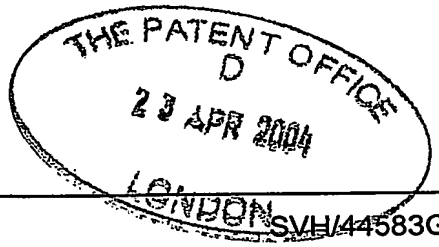

1. Your reference SVH/44583GB2

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4. Title of the invention Methods for Preparing Pharmaceutical Compositions

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6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and the or each application number

Country	Priority application number	Date of filing

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Number of earlier application	Date of Filing

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11. I/We request the grant of a patent on the basis of this application.

Signature: Venner Shipley RCA

Date: 23 April 2004

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Methods for Preparing Pharmaceutical Compositions

The present invention relates to improvements in dry powder formulations comprising a pharmaceutically active agent for administration by inhalation, and in particular to methods of preparing dry powder compositions with improved properties.

The lung provides an obvious target for local administration of formulations which are intended to cure or alleviate respiratory or pulmonary diseases, such as cystic fibrosis (CF), asthma, lung cancer, etc. The lung also provides a route for delivery of systemically acting formulations to the blood stream, for example, for delivery of active agents which are not suitable for oral ingestion, such as agents that degrade in the digestive tract before they can be absorbed, and those requiring an extremely rapid onset of their therapeutic action.

It is well established that delivering pharmaceutically active agents to the lung by pulmonary inhalation of a dry powder has a number of advantages which make this an attractive mode of delivery.

However, the delivery of dry powder particles of pharmaceutical products to the respiratory tract presents certain problems. The inhaler device, which is preferably a bespoke device, such as a dry powder inhaler (DPI), should deliver the maximum possible proportion of the particles of pharmaceutically active agent (active particles) to the lungs. Indeed, a significant proportion of the active particles should be deposited in the lower lung, preferably even at the low inhalation capabilities to which some patients, especially asthmatics, are limited. However, when using many dry powder formulations, it has been found that frequently only a small proportion (often only about 10%) of the active particles that leave the device on actuation are actually deposited in the lower lung. As a result, much work has been done on improving dry powder formulations to enhance the delivery of the active particles to the lower respiratory tract or deep lung.

The type of dry powder inhaler used can influence the proportion of the active particles delivered to the lung, as different types of inhaler devices provide different air flow conditions which lead to the active particles reaching the respiratory tract. Also, the physical properties of the powder affect both the efficiency and reproducibility of delivery of the active particles and the site of deposition in the respiratory tract.

On exit from the inhaler device, the active particles should form a physically and chemically stable aerocolloid which remains in suspension until it reaches a conducting bronchiole or smaller branching of the pulmonary tree or other absorption site, preferably in the lower lung. Once at the absorption site, the active particles should be capable of efficient collection by the pulmonary mucosa with as few as possible active particles being exhaled from the absorption site.

When delivering a formulation to the lung for local or systemic action, the size of the active particles within the formulation is very important in determining the site of the absorption in the body.

For formulations to reach the deep lung or the blood stream via inhalation, the active agent in the formulation must be in the form of very fine particles, for example, having a mass median aerodynamic diameter (MMAD) of less than 10μm. It is well established that particles having an MMAD of greater than 10μm are likely to impact on the walls of the throat and generally do not reach the lung. Particles having an MMAD in the region of 5 to 2μm will generally be deposited in the respiratory bronchioles whereas particles having an MMAD in the range of 3 to 0.05μm are likely to be deposited in the alveoli or be absorbed into the bloodstream.

Preferably, for delivery to the lower respiratory tract or deep lung, the MMAD of the active particles is not more than 10μm, and preferably not more than 5μm, more preferably not more than 3μm, and may be less than 2μm, less than 1.5μm or less than 1μm. Ideally, at least 90% by weight of the active particles in a dry powder formulation should have an aerodynamic diameter of not more than 10μm,

preferably not more than 5μm, more preferably not more than 3μm, not more than 2μm or not more than 1μm.

When dry powders are produced using conventional processes, the active particles will vary in size, and often this variation can be considerable. This can make it difficult to ensure that a high enough proportion of the active particles are of the appropriate size for administration to the correct site. It is therefore desirable to have a dry powder formulation wherein the size distribution of the active particles is as narrow as possible. This will improve dose efficiency and reproducibility.

Fine particles, that is, those with an MMAD of less than 10μm and smaller tend to be increasingly thermodynamically unstable as their surface area to volume ratio increases, which provides an increasing surface free energy with this decreasing particle size, and consequently increases the tendency of particles to agglomerate and the strength of the agglomerate. In the inhaler, agglomeration of fine particles and adherence of such particles to the walls of the inhaler are problems that result in the fine particles leaving the inhaler as large, stable agglomerates, or being unable to leave the inhaler and remaining adhered to the interior of the inhaler, or even clogging or blocking the inhaler.

The uncertainty as to the extent of formation of stable agglomerates of the particles between each actuation of the inhaler, and also between different inhalers and different batches of particles, leads to poor dose reproducibility. Furthermore, the formation of agglomerates means that the MMAD of the active particles can be vastly increased, with agglomerates of the active particles not reaching the required part of the lung.

The metered dose (MD) of a dry powder formulation is the total mass of active agent present in the metered form presented by the inhaler device in question. For example, the MD might be the mass of active agent present in a capsule for a Cyclohaler (trademark), or in a foil blister in an Aspirair (trademark) device.

The emitted dose (ED) is the total mass of the active agent emitted from the device following actuation. It does not include the material left on the internal or external surfaces of the device, or in the metering system including, for example, the capsule or blister. The ED is measured by collecting the total emitted mass from the device in an apparatus frequently identified as a dose uniformity sampling apparatus (DUSA), and recovering this by a validated quantitative wet chemical assay.

The fine particle dose (FPD) is the total mass of active agent which is emitted from the device following actuation which is present in an aerodynamic particle size smaller than a defined limit. This limit is generally taken to be 5μm if not expressly stated to be an alternative limit, such as 3μm, 2μm or 1μm, etc. The FPD is measured using an impactor or impinger, such as a twin stage impinger (TSI), multi-stage impinger (MSI), Andersen Cascade Impactor or a Next Generation Impactor (NGI). Each impactor or impinger has a pre-determined aerodynamic particle size collection cut points for each stage. The FPD value is obtained by interpretation of the stage-by-stage active agent recovery quantified by a validated quantitative wet chemical assay where either a simple stage cut is used to determine FPD or a more complex mathematical interpolation of the stage-by-stage deposition is used.

The fine particle fraction (FPF) is normally defined as the FPD divided by the ED and expressed as a percentage. Herein, the FPF of ED is referred to as FPF(ED) and is calculated as FPF(ED) = (FPD/ED) x 100%.

The fine particle fraction (FPF) may also be defined as the FPD divided by the MD and expressed as a percentage. Herein, the FPF of MD is referred to as FPF(MD), and is calculated as FPF(MD) = (FPD/MD) x 100%.

The tendency of fine particles to agglomerate means that the FPF of a given dose is often highly unpredictable and a variable proportion of the fine particles will be administered to the lung, or to the correct part of the lung, as a result.

In an attempt to improve this situation and to provide a consistent FPF and FPD, dry powder formulations may include additive material.

The additive material is intended to decrease the cohesion between particles in the dry powder formulation. It is thought that the additive material interferes with the weak bonding forces between the small particles, helping to keep the particles separated and reducing the adhesion of such particles to one another, to other particles in the formulation if present and to the internal surfaces of the inhaler device. Where agglomerates of particles are formed, the addition of particles of additive material decreases the stability of those agglomerates so that they are more likely to break up in the turbulent air stream created on actuation of the inhaler device, whereupon the particles are expelled from the device and inhaled. As the agglomerates break up, the active particles return to the form of small individual particles which are capable of reaching the lower lung.

In the prior art, dry powder formulations are discussed which include additive material in particulate form, the particles generally being of a size comparable to the size of the fine active particles. In some embodiments, the additive material may form a coating, generally a discontinuous coating, on the active particles and/or any carrier particles.

Preferably, the additive material is an anti-adherent material and it will tend to reduce the cohesion between particles and will also prevent fine particles becoming attached to the inner surfaces of the inhaler device. Advantageously, the additive material is an anti-friction agent or glidant and will give better flow of the pharmaceutical composition in the inhaler. The additive materials used in this way may not necessarily be usually referred to as anti-adherents or anti-friction agents, but they will have the effect of decreasing the cohesion between the particles or improving the flow of the powder. The additive materials are often referred to as force control agents (FCAs) and they usually lead to better dose reproducibility and higher fine particle fractions.

Therefore, an FCA, as used herein, is an agent whose presence on the surface of a particle can modify the adhesive and cohesive surface forces experienced by that

particle, in the presence of other particles. In general, its function is to reduce both the adhesive and cohesive forces.

In general, the optimum amount of additive material to be included in a dry powder formulation will depend on the chemical composition and other properties of the additive material and of the active material, as well as upon the nature of other particles such as carrier particles, if present. In general, the efficacy of the additive material is measured in terms of the fine particle fraction of the composition.

Known additive materials usually consist of physiologically acceptable material, although the additive material may not always reach the lung. For example, where the additive particles are attached to the surface of carrier particles, they will generally be deposited, along with those carrier particles, at the back of the throat of the user.

Preferred additive materials used in the prior art dry powder formulations include amino acids, peptides and polypeptides having a molecular weight of between 0.25 and 1000 kDa and derivatives thereof, dipolar ions such as zwitterions, lipids and phospholipids such as lecithin, and metal stearates such as magnesium stearate.

In a further attempt to improve this situation and to provide a consistent FPF and FPD, dry powder formulations often include coarse carrier particles of excipient material mixed with fine particles of active material. Rather that sticking to one another, the fine active particles tend to adhere to the surfaces of the coarse carrier particles whilst in the inhaler device, but are supposed to release and become dispersed upon actuation of the dispensing device and inhalation into the respiratory tract, to give a fine suspension. The carrier particles preferably have MMADs greater than 60μm.

The inclusion of coarse carrier particles is also very attractive where very small doses of active agent are dispensed. It is very difficult to accurately and reproducibly dispense very small quantities of powder and small variations in the amount of powder dispensed will mean large variations in the dose of active agent

where the powder comprises mainly active particles. Therefore, the addition of a diluent, in the form of large excipient particles will make dosing more reproducible and accurate.

Carrier particles may be of any acceptable excipient material or combination of materials. For example, the carrier particles may be composed of one or more materials selected from sugar alcohols, polyols and crystalline sugars. Other suitable carriers include inorganic salts such as sodium chloride and calcium carbonate, organic salts such as sodium lactate and other organic compounds such as polysaccharides and oligosaccharides. Advantageously, the carrier particles are of a polyol. In particular, the carrier particles may be particles of crystalline sugar, for example mannitol, dextrose or lactose. Preferably, the carrier particles are of lactose.

Advantageously, substantially all (by weight) of the carrier particles have a diameter which lies between 20μm and 1000μm, more preferably 50μm and 1000μm. Preferably, the diameter of substantially all (by weight) of the carrier particles is less than 355μm and lies between 20μm and 250μm.

Preferably at least 90% by weight of the carrier particles have a diameter between from 60μm to 180μm. The relatively large diameter of the carrier particles improves the opportunity for other, smaller particles to become attached to the surfaces of the carrier particles and to provide good flow and entrainment characteristics and improved release of the active particles in the airways to increase deposition of the active particles in the lower lung.

The ratios in which the carrier particles (if present) and composite active particles are mixed will, of course, depend on the type of inhaler device used, the type of active particles used and the required dose. The carrier particles may be present in an amount of at least 50%, more preferably 70%, advantageously 90% and most preferably 95% based on the combined weight of the composite active particles and the carrier particles.

However, a further difficulty is encountered when adding coarse carrier particles to a composition of fine active particles and that difficulty is ensuring that the fine particles detach from the surface of the large particles upon actuation of the delivery device.

The step of dispersing the active particles from other active particles and from carrier particles, if present, to form an aerosol of fine active particles for inhalation is significant in determining the proportion of the dose of active material which reaches the desired site of absorption in the lungs. In order to improve the efficiency of that dispersal it is known to include in the composition additive materials, including FCAs of the nature discussed above. Compositions comprising fine active particles and additive materials are disclosed in WO 97/03649 and WO 96/23485.

In light of the foregoing problems associated with known dry powder formulations, even when including additive material and/or carrier particles, it is an aim of the present invention to provide dry powder compositions which have physical and chemical properties which lead to an enhanced FPF and FPD. This leads to greater dosing efficiency, with a greater proportion of the dispensed active agent reaching the desired part of the lung for achieving the required therapeutic effect.

In particular, the present invention seeks to optimise the preparation of particles of active agent used in the dry powder composition by engineering the particles making up the dry powder composition and, in particular, by engineering the particles of active agent. It is an aim of the present invention to provide particles of active agent which are smaller than those produced by known methods or processes. It is also an aim to provide particles with a particle make-up and morphology which will produce high FPF and FPD results.

Whilst the FPF and FPD of a dry powder formulation are dependent on the nature of the powder itself, these values are also influenced by the type of inhaler used to dispense the powder. For example, the FPF obtained using a passive device will

tend not to be as good as that obtained with the same powder but using an active device, such as an Aspirair (trade mark) device (see WO 01/00262 and GB2353222).

It is an aim of the present invention to optimise the powder properties, so that the FPF and FPD are improved compared to those obtained using known powder formulations, regardless of the type of device used to dispense the composition of the invention.

It is a particular aim of the present invention to provide a dry powder formulation which has an FPF of at least 40%. Preferably, the FPF(ED) will be between 60 and 99%, more preferably between 70 and 99%, more preferably between 80 and 99% and even more preferably between 90 and 99%. Furthermore, it is desirable for the FPF(MD) to be at least 40%. Preferably, the FPF(MD) will be between 40 and 99%, more preferably between 50 and 99%, more preferably between 60 and 99%, and more preferably between 70 and 99% and even more preferably between 80 and 99%.

The present invention is described below in detail, with reference to the following drawings:

Figure 1 shows a schematic set-up of a conventional type spray drying apparatus with a 2-fluid nozzle;

Figures 2A-2D are SEM micrographs of 2-fluid nozzle spray dried powders which were co-spray dried with increasing amounts of l-leucine (0%, 5%, 25% and 50% w/w), without secondary drying;

Figures 2E-2H are SEM micrographs of 2-fluid nozzle spray dried powders which were co-spray dried with increasing amounts of l-leucine (2%, 5%, 10% and 50% w/w), after secondary drying;

Figure 3 shows a schematic diagram of an ultrasonic nebuliser producing fine droplets;

Figure 4 shows a schematic set-up of a spray drier incorporating an ultrasonic nebuliser;

Figures 5A and 5B show SEM micrographs of spray dried nebulised heparin alone and with 10% w/w leucine, without secondary drying;

Figure 6 shows a typical size distribution curve of three repeated tests of spray dried nebulised heparin (with no FCA);

Figures 7A-7C show a comparison between particle size distribution curves of 2-fluid nozzle spray dried powders and ultrasonic nebulised powders comprising a blend of heparin and leucine (2% w/w, 5% w/w and 10% w/w); and

Figure 8 shows a comparison between particle size distribution curves of secondary dried and not secondary dried powders. The powder used was heparin with leucine (10% w/w).

In the past, several methods have been used to make fine particles of active material. The material may be ground or milled to form particles with the desired size. Alternatively, the particles may be made by spray drying techniques. Some other alternatives methods include supercritical fluid, precipitation and crystallisation.

The present invention is concerned with improving the conventional spray drying techniques, in order to produce active particles with enhanced chemical and physical properties so that they perform better when dispensed from a DPI than particles formed using conventional spray drying techniques giving greater FPF and FPD for given device. The improved results are preferably achieved regardless of whether the DPI used to dispense the powder is an active inhaler or a passive inhaler.

Spray drying is a well-known and widely used technique for producing particles of material. To briefly summarise, the material to be made into particles is dissolved or dispersed in a liquid or can be made into a liquid which is sprayed through a nozzle under pressure to produce a mist or stream of fine droplets. These fine droplets are usually exposed to heat which rapidly evaporates the moisture in the droplets, leaving dry powder particles. The process is relatively cheap and simple.

A standard method for producing particles of an active material involves using a conventional spray dryer, such as a Büchi B-191 under a "standard" set of parameters. Such standard parameters are set out in Table 1.

Table 1: "Standard" parameters used in spray drying using the Büchi B-191 spray dryer (Büchi two fluid nozzle, internal setting, 0.7mm mixing needle and cap, 100% aspirator setting)

Atomisation pressure	Inlet temp	Outlet temp	Total solid conc'n (% w/w) in solvent	Solvent (host liquid)	Feed rate (ml/min)
5 - 6 bar	150°C	~100°C	1	Aqueous	5

There are a number of problems associated with the spray drying of pharmaceutically active agents. Firstly, there is the problem that the conventional spray drying processes and apparatus have a relatively low output for very fine powders (e.g. <10μm) and therefore are not particularly well suited to large scale production of pharmaceuticals. Secondly, most spray drying involves exposing the spray dried material to high temperatures, in order to ensure that the necessary evaporation takes place so that the dry particles are formed. Some temperature-sensitive active agents can be adversely affected by exposure to the temperatures used in conventional spray drying methods. A further disadvantage associated with conventional spray drying techniques is that the particles produced can have a broad range of particle sizes. This means that whilst some of the particles produced have the desired particle size, a proportion of the particles will not. Furthermore, this often results in a considerable quantity of the material, by mass, being larger than the desired particles size for delivery to the required site in the lung.

Despite the foregoing, spray drying pharmaceutically active agents is still an accepted method of producing particles which are of a size suitable for administration by dry powder inhalation to the lungs.

Whilst spray drying can produce particles of a small enough size to be inhaled into the deep lung, these particles will frequently suffer from the agglomeration problems discussed above. Therefore, it will be necessary to modify the dry powder particles, in order to achieve good dispersion required for accurate dosing.

This modification may involve the simple addition of a force control agent to the spray dried particles of active material, as discussed above. Alternatively, the force control agent may be spray dried together with the active agent.

The co-spray drying of an active material and a force control agent has been disclosed in the prior art, albeit without proper recognition that the additives in question act as force control agents. For example, in WO 96/32149 (Inhale Therapeutic Systems), the co-spray drying of a pharmaceutically active agent and a carrier is proposed. The carrier is said to act as a bulking agent and may be, for example, a carbohydrate or an amino acid. There is little discussion of the spray drying technique, aside from that it involves the spray drying of an aqueous solution and conventional spray drying apparatus. Whilst it is suggested that the carrier may assist dispersal of the resultant spray dried particles, its inclusion does not seek to optimise this effect. The carrier is included in varying amounts and it would appear that this material is evenly distributed throughout the particles, with only a small proportion, if any, of the carrier material being present on the surfaces of the particles.

The inventors have now discovered that co-spray drying an active agent with a force control agent under specific conditions can result in particles with excellent properties which perform extremely well when administered by a DPI for inhalation into the lung.

In particular, it has been found that manipulating or adjusting the spray drying process can result in the force control agent being largely present on the surface of the particles. This clearly means that the force control agent will be able to reduce the tendency of the particles to agglomerate.

This allows dry powder compositions to be prepared which comprise co-spray dried active particles that exhibit a fine particle fraction (<5μm) of at least 40%. Preferably, the FPF(ED) will be between 60 and 99%, more preferably between 70 and 99%, more preferably between 80 and 99% and even more preferably between 90 and 99%. Furthermore, it is desirable for the FPF(MD) to be at least 40%. Preferably, the FPF(MD) will be between 40 and 99%, more preferably between 50 and 99%, more preferably between 60 and 99%, and more preferably between 70 and 99% and even more preferably between 80 and 99%.

Preferably, for delivery to the lower respiratory tract or deep lung, the MMAD of the spray dried active particles is not more than 10μm, and preferably not more than 5μm, more preferably not more than 3μm, and may be less than 2μm, less than 1.5μm or less than 1μm. Ideally, at least 90% by weight of the active particles in a dry powder formulation should have a diameter (equivalent sphere) of not more than 10μm, preferably not more than 8μm, more preferably not more than 6μm, not more than 5μm or not more than 2.5μm.

The effects of co-spray drying an active agent and a FCA are illustrated in the following discussion of various experiments and the results obtained. The experiments look at various variable factors in the spray drying process and investigate their effects on the nature and performance of the resultant particles.

In the experiments, the active agent used is heparin. The reason for selecting this active agent to illustrate and test the present invention is that heparin is a "sticky" compound and this tends to have a detrimental effect on the FPF and FPD of the dry powder. Therefore, obtaining good values of FPF and FPD using heparin is an indication that the compositions really do exhibit good and improved properties, regardless of the "difficult" nature of the active agent included.

Unless otherwise indicated, the FPF(ED) and FPF(MD) figures given in the following sections of this specification were obtained by firing capsules, filled with approximately 20mg of material, from a Monohaler into a multi stage liquid impinger (MSLI), at a flow rate of 90lpm, or a twin stage or rapid twin stage impinger (TSI or rTSI) at 60lpm. The fine particle fraction determination from a Miat MonoHaler device into a Multi Stage Liquid Impinger (MSLI) and a TSI, using the method defined in the European Pharmacopoeia 4th edition 2002, or the 'Rapid Twin Stage Impinger' (rTSI) method outlined previously (M. Tservistas et al., A Novel TSI Method for Rapid Assessment of Inhaleable Dry Powder Formulations, Proc. Aerosol Society Conference, Bath, 2001).

The "delivered dose" or "DD", which is referred to in some of the following sections, is the same as the emitted dose or ED (as defined above).

In order to illustrate how the various variable factors of the spray drying process affects the properties of the resultant spray dried particles, firstly the effect of adjusting the solid concentration of active agent was investigated. The active agent was spray dried (without an FCA) using the standard parameters as shown in Table 1, but the solid concentration of active agent was increased from 1% w/w to 2 and 5% w/w total solids. The effects of these changes on the FPFs were then investigated and the results were as follows.

Table 2: FPF (%) less than 5μm of the delivered dose (DD) for spray dried heparin using "standard" spray drying parameters

Description	Test	FPF <5μm (DD) (%)
1% w/w heparin	MSLI	17.0
1% w/w heparin	TSI	20.3

The FPF for heparin spray dried alone, that is, without a co-spray dried FCA, using the "standard" spray drying parameters (see Table 1) was 17-20% as shown in Table 2. Testing was done with both a multi stage liquid impinger (MSLI) and a twin stage impinger (TSI).

Table 3: FPF (%) less than 5μm of DD for heparin spray dried from increasing solid concentrations

Description	Test	FPF <5μm (DD) (%)
2% w/w heparin	rTSI	21.3
5% w/w heparin	rTSI	8.3

Increasing the solid concentration of heparin from 1% w/w (Table 2) to 5% w/w (Table 3) caused a large reduction in FPF of heparin from approximately 20% FPF to 8.3%, when tested using a rapid-TSI. 2% w/w solid content did not seem to have an effect on FPF.

Thus, increasing the solid content of the feed solution did not improve the FPF of the active particles. Increasing the solid content as high as 5% w/w reduced the FPF by more than 10%. Increasing the solid content of a feedstock without changing any of the other parameters generally causes an increase in particle size, as each droplet will have a greater mass of solid which results in larger particles upon drying.

Accordingly, although a solid content of up to 10% w/w active agent, and in some cases as much as 25% w/w active agent, can be used, it is preferred for up to 5% w/w, and more preferably up to 2% w/w active agent to be used in the spray drying process of the present invention. It is also preferred for at least 0.05% w/w, and more preferably for at least 0.5% w/w to be employed for practical purposes of production rate.

A further variable factor in the spray drying process is the nature of the feedstock, which may be a solution or a suspension and which can comprise a variety of different solvents or combinations thereof.

In some embodiments, all or at least a proportion of the active agent and/or FCA is or are in solution in the host liquid before being subjected to spray drying. Substantially all of the active agent and FCA can be in solution in the host liquid before being subjected to spray drying.

The active agent is preferably at least 1.5, 2, 4 and, more preferably, at least 10 times more soluble than the FCA in the host liquid at the spraying temperature and pressure. In preferred embodiments, this relationship exists at a temperature between 30 and 60°C and atmospheric pressure. In other embodiments, this relationship exists at a temperature between 20 to 30°C and atmospheric pressure, or, preferably, at 20°C and atmospheric pressure.

The FCA may include one or more water soluble substances. This helps absorption of the substance by the body if the FCA reaches the lower lung. The FCA may include dipolar ions, which may be zwitterions.

Alternatively, the FCA may comprise a substance which is not soluble in water or which is only poorly soluble in water. Where such an FCA is used, it may be advantageous to include further agents to the mixture to be spray dried which will assist solubilising the FCA. For example, the FCA used could be magnesium stearate, which is only slightly soluble in water. However, the addition of an acid will help to solubilise the magnesium stearate and, as the acid will evaporate during the spray drying process, the resultant particles will not suffer from any "contamination" from the acid. Nevertheless, the use of a water soluble FCA is preferred, as the spray drying system is simpler and probably more predictable.

The host liquid preferably includes water. The liquid can employ water alone as a solvent or it may also include an organic co-solvent, or a plurality of organic co-solvents. A combination of water and one or more organic co-solvents is especially useful with active agents and FCAs that are insoluble or substantially insoluble in water alone. Preferred organic co-solvents include methanol, ethanol, propan-1-ol, propan1-2-ol and acetone, with ethanol being the most preferred.

In one embodiment of the present invention, the host liquid consists substantially of water. The use of this host liquid reduces any environmental cost or toxicological complications, or explosive risk. Hence, a host liquid consisting essentially of water provides a significant practical advantage and reduces the process costs.

If an organic solvent is present in the host liquid, it should be selected so that it produces a vapour which is significantly below any explosive or combustion limit. Also, preferably, the spraying composition does not include any blowing agent, such as ammonium carbonate or a halogenated liquid.

The effect of spray drying an active agent with various organic solvents was evaluated. The "standard" parameters as outlined in Table 1 were used to spray dry heparin, with the only difference being that the heparin was spray dried from 10%

w/w organic solvent (propan-1-ol, methanol or ethanol) in water. The results are set out in Table 4.

Table 4: FPF (%) less than 5μm of DD for heparin spray dried from an organic solvent.

Spray drying feedstock % w/w heparin	Solvent % w/w	Test	FPF <5μm (DD) (%)
1	10% methanol	MSLI	2.3
1	10% ethanol	MSLI	6.2
1	10% propan-1-ol	MSLI	2.0

Spray drying 1% w/w heparin from 10% methanol, ethanol and propan-1-ol resulted in a lowering of FPF (Table 4) from approximately 20% when spray dried from aqueous solvent using identical parameters (shown in Table 2) to 2-6% FPF.

One might expect that adding an organic solvent to the feedstock would cause an increase of the FPF, as a result of a reduction in the viscosity of the feedstock, and a lower energy input being required to generate smaller particles. However, the results obtained from 2-fluid nozzle spray drying of heparin from feedstocks containing 10% organic solvent (Table 4) show a reduction in FPF.

Variations in the FPFs may be caused by the effect that the solvent has on the positioning of any hydrophobic moieties of the drug or FCA whilst in the spray drying solution or suspension. The hydrophobic moieties are thought to have the significant force controlling effect. The exposure of a hydrophobic surface is believed to minimise any potential polar forces increasing surface adhesion, such as hydrogen bonds or permanent dipole effects, leaving only the ubiquitous weak London forces. The presence of these hydrophobic moieties on the surface of the particles is therefore important if the cohesion of the powder particles is to be limited, to provide better FPF performance.

When the FCA is in an aqueous solvent, the hydrophobic moieties will be repelled from the interior of the droplet, as the thermodynamics of the system will tend to drive a minimum interaction of these groups with the polar aqueous phase. The

positioning of these moieties is therefore dictated by the nature of the solvent and this, in turn, affects the positioning of these groups in the eventual spray dried particles. When the aqueous solution of active agent and FCA is spray dried, it may be that the hydrophobic moieties are more likely to be positioned on the surfaces of the particles than if the active agent and FCA are dissolved in an organic solvent, such as ethanol or methanol.

As a further test of the parameters which might affect the nature of the spray dried particles, an active agent was spray dried using the standard parameters used above (Table 1), but the effect of temperature on the particles produced was investigated by spray drying with inlet temperatures of 75°C to 220°C. The results are set out in Table 5.

Table 5: FPF (%) less than 5µm of DD for heparin spray dried using different inlet temperatures.

Inlet temperature	Approx. outlet temperature	Test	FPF <5µm (DD) (%)
220°C	135°C	MSLI	17.5
75°C	35°C	rTSI	22.5

Thus, it can be seen that spray drying heparin at a higher or lower inlet temperature relative to the "standard" 150°C normally used did not offer a substantial improvement in FPF.

A preferable range for the inlet temperature is 40°C to 300°C, preferably 75°C to 220°C. A preferable range for the outlet temperature is 20°C to 200°C, preferably 35°C to 135°C.

The effects of co-spray drying an active agent with varying amounts of the l-leucine, a FCA, from aqueous solution were then studied. Standard Büchi spray drying parameters were used, as shown in Table 1. L-leucine was included in the solution of heparin such that the percentage of l-leucine ranged from 2-50% w/w. The results are set out in Table 6.

1% total solids solutions were sprayed from a 2-fluid nozzle into a Büchi spray drier. Blends of heparin and l-leucine were prepared at different weight percentages of l-leucine. Powders of 2%, 5%, 10%, 25% and 50% w/w l-leucine were prepared. The spray drier feed flow rate was 120 ml/hr, the inlet temperature was 150°C, and flush nozzle setting was used. The schematic set-up of the two-fluid nozzle spray drier is shown in Figure 1.

Table 6: FPF (%) less than 5µm of DD for heparin co-spray dried with l-leucine.

Spray drying feedstock % w/w	Co-spray drying with l-leucine % w/w	Test	FPF <5µm (DD) (%)
1	2%	rTSI	20.0
1	5%	MSLI	32.8
1	10%	MSLI	30.8
1	25%	MSLI	35.4
1	50%	MSLI	51.7

The results show that increasing the percentage of l-leucine included in the feedstock for spray drying resulted in a steady improvement in FPF from approximately 20% FPF with 2% leucine, to 50% FPF with 50% leucine (Table 6).

A further MSLI study was conducted using a feed rate of 300 ml/hr.

20mg of powder was dispersed in each case. The results set out in Table 7 indicate an improvement of FPF with addition of a FCA, although the FPD does not improve with the addition of more than 10% l-leucine due to the relative reduction of the heparin content.

Table 7: MSLI study of co-spray dried heparin and varying concentrations of leucine

Formulation	Test	Emitted dose (ED) (mg)	FPF% (ED)	FPD (mg)
Heparin (0% leucine)	MSLI	10	17	1.8
Heparin + leucine (5% w/w)	MSLI	11	33	3.6
Heparin + leucine (10% w/w)	MSLI	13	31	3.9

Heparin + leucine (25% w/w)	MSLI	10	35	3.7
Heparin + leucine (50% w/w)	MSLI	6	52	3.0

Thus, the increased FPF is achieved even at low amounts of FCA. Whilst the active agent may be spray dried with from 0.1 to 50% w/w FCA to active agent, smaller amounts of FCA are preferred, in order to reduce the risk of toxicity problems. Preferably, the amount of FCA is no more than 10% w/w, more preferably, it is no more than 5% w/w, no more than 3% w/w, no more than 2% w/w or no more than 1% w/w.

In some embodiments, the FCA is an amino acid, and preferably the FCA is hydrophobic amino acid. One or more of the following amino acids may be used: leucine, preferably l-leucine, isoleucine, lysine and cysteine. Most preferably, the active agent is co-spray dried with l-leucine.

It has been found that co-spray drying an active agent with an FCA, and in particular with l-leucine, isoleucine, lysine and cysteine, leads to significant changes in the particle cohesion, greatly enhancing the properties of the dry powder when administered by pulmonary inhalation.

Where the spray drying takes place under "standard" parameters and using conventional spray drying apparatus, it has been found that spray drying an active agent with an FCA can lead to non-spherical particle morphology. At low concentrations of FCA, the surfaces of the particles show dimples or depressions. As the amount of co-spray dried FCA is increased, these dimples become more extreme, with the particles eventually having a shrivelled or wrinkled surface, the net effect therefore is the formulation of less dense particles.

The morphology of the particles was viewed using scanning electron micrographs (SEMs).

SEM micrographs of 2-fluid nozzle spray dried powders (Figures 2A-D) illustrate a clear relationship between the increasing percentage of l-leucine and an increasingly

dimpled or wrinkled surface of the particles. The particles with the highest l-leucine content appear to be extremely wrinkled and, in selected cases, may even burst as an extreme result of "blowing", a phenomenon whereby the particles form a shell or skin which inflates due to the evaporation of the solvent, creating a raised internal vapour pressure and then may collapse or burst.

Droplets from the two fluid nozzle are initially dried at a relatively high rate during spray drying. This creates a viscous layer of material around the exterior of the liquid droplet. As the drying continues, the viscous layer is firstly stretched (like a balloon) by the increased vapour pressure inside the viscous layer as the solvent evaporates. The solvent vapour diffuses through the growing viscous layer until it is exhausted and the viscous layer then collapses, resulting in the formation of craters in the surface or wrinkling of the particles.

Figure 2A is an SEM micrograph of 2-fluid nozzle spray dried heparin. The particles are generally spherical in shape and the surfaces are substantially smooth. However, the particles each have one (smooth) crater or dimple in their surface.

Figure 2B is an SEM micrograph of 2-fluid nozzle spray dried heparin with 5% leucine. The particles now exhibit more dimples or craters on their surface. The particles still have a generally smooth surface.

Figure 2C is an SEM micrograph of 2-fluid nozzle spray dried heparin with 25% leucine. With the increase in FCA, the surface of the particles no longer appears smooth and the generally spherical shape has disappeared. The particles have a shrivelled, wrinkled appearance.

Figure 2D is an SEM micrograph of 2-fluid nozzle spray dried heparin with 50% leucine. The shrivelling observed in the particles of Figure 2C has become more pronounced and the particles appear to have inflated and then collapsed, looking like extremely wrinkled particles.

The net effect of the inflation, stretching of the skin and deflation is the creation of significant numbers of craters and wrinkles or folds on the particle surface, which consequently results in a relatively low density particle which occupies a greater volume than a smooth-surfaced particle.

This change in the surface morphology of these co-spray dried particles may contribute to reduced cohesion between the particles. Particles of pure active material are generally spherical in shape, as seen in Figure 2A. It has been argued that increased particle surface roughness or rugosity, such as is caused by surface wrinkles or craters, results in reduced particle cohesion and adhesion by minimising the surface contact area between particles.

However, it has surprisingly been found that it is advantageous not to produce severely dimpled or wrinkled particles, as these can yield low density powders, with very high voidage between particles. Such powders occupy a large volume relative to their mass as a consequence of this form, and can result in packaging problems, i.e., much larger blisters or capsules are required for a given mass of powder.

Advantageously, powders according to the present invention have a tapped density of more than 0.1g/cc, more than 0.2g/cc, more than 0.3g/cc, more than 0.4g/cc, or more than 0.5g/cc.

It has also been speculated that this particle morphology may even help the particles to fly when they are expelled for the inhaler device. This means that more of the active particles are capable of reaching the lower respiratory tract or deep lung. Despite this speculation relating to the benefits of the irregular shapes of the particles to be inhaled, the inventors actually feel that the chemical nature of the particle surfaces may be even more influential on the performance of the particles in terms of FPF, ED, etc.. In particular, it is thought that the presence of hydrophobic moieties on the surface of particles is thought to be more significant in reducing cohesion that the presence of craters or dimples. As mentioned above, it is believed that the solvent used in the feedstock may be able to influence the chemical properties of the particle surfaces. Therefore, contrary to the suggestion

in the prior art, it is not necessary to seek to produce extremely dimpled or wrinkled particles in order to provide good FPF values.

Next, the effect of spray drying an active agent with various excipients was investigated. Standard spray drying parameters as shown in Table 1 were used and the various excipients tested were lactose, dextrose, mannitol and human serum albumin (HSA). The excipients were co-spray dried with heparin from aqueous solution. Between 5-50% w/w of the excipients were included, with total solid content not exceeding 1% w/w of the solution.

Table 8: FPF (%) less than 5μm of DD for heparin co-spray dried with excipients.

Spray drying feedstock % w/w	Co-spray drying excipient % w/w	Test	FPF <5μm (DD) (%)
1	5% lactose	rTSI	7.0
1	20% lactose	rTSI	5.3
1	50% lactose	rTSI	10.3
1	5% dextrose	rTSI	11.0
1	50% dextrose	rTSI	1.7
1	5% mannitol	rTSI	14.0
1	20% mannitol	rTSI	11.3
1	5% HSA	rTSI	34.0
1	50% HSA	rTSI	28.0

Inclusion of lactose (5-50%), dextrose (5-50%) and mannitol (5-20%) did not improve the FPF (Table 8). In fact, for all of these excipients, FPFs fell to below the "standard" 20% for spray dried heparin. However, inclusion of 5% HSA gave an improvement.

As the presence of the HSA in the active particle clearly reduces the particle cohesion, thereby increasing the FPF, HSA may be considered, for the purpose of the present invention, to be a FCA. However, in some embodiments of the invention, the FCA used is preferably not HSA.

It is believed that the ability of HSA to act as an FCA when co-spray dried as described above may be due to the arrangement of the hydrophobic moieties of the HSA on the surface of the spray dried particles. As discussed above, the positioning of hydrophobic groups on the surface of the spray dried particles is considered to be very important and can affect the cohesiveness and adhesiveness of the particles in a dry powder formulation. Proteins, such as HSA, tend to have hydrophobic parts of their constituent amino acids which allow them to act as FCAs under the appropriate conditions. Indeed, in one embodiment of the present invention, where the active agent is a protein, under the correct spray drying conditions, the active agent may itself act as an FCA, thereby avoiding the need to spray dry the protein with a separate FCA. The protein must be spray dried in a manner that will allow the hydrophobic moieties to be arranged on the surface of the resultant particles. Therefore, the host solution is preferably an aqueous solution. Additionally, the drying of the particles should occur at a rate which allows the movement of the hydrophobic moieties or retention of the moieties at the surface.

Thus, according to one aspect of the present invention, a method is provided for producing spray dried particles comprising a protein as both the active agent and an FCA. The particles exhibit FPF(ED) and FPF(MD) which is better than those exhibited by conventionally spray dried particles of protein, as a result of the hydrophobic moieties arranged on the surface of the spray dried particles according to the present invention.

Alternative Droplet Formation

It has further been discovered that the FPF and FPD of the dry powder formulation is also affected by the means used to create the droplets which are spray dried. Different means of forming droplets can affect the size and size distribution of the droplets, as well as the velocity at which the droplets travel when formed and the gas flow around the droplets. In this regard, the velocity at which the droplets travel when formed and the gas (which is usually air) flow around the droplets can significantly affect size, size distribution and shape of resulting dried particles.

This aspect of the spray drying process is therefore important in the inventors' attempts to engineer particles with chemical and physical properties that provide good performance which the particles are administered via pulmonary inhalation.

It has been found that the formation of the droplets in the spray drying process may be controlled, so that droplets of a given size and of a narrow size distribution may be formed. Furthermore, controlling the formation of the droplets can allow control of the air flow around the droplets which, in turn, can be used to control the drying of the droplets and, in particular, the rate of drying. Controlling the formation the droplets may be achieved by using alternatives to the conventional 2-fluid nozzles, especially avoiding the use of high velocity air flows. The following discussion of the use of alternative droplet forming means can be used in combination with all of the foregoing factors which provide improvements in the performance of the spray dried particles, as will become clear.

According to another aspect of the present invention, a method of preparing a dry powder composition is provided, wherein the active agent is spray dried using a spray drier comprising a means for producing droplets moving at a controlled velocity and of a predetermined droplet size. The velocity of the droplets is preferably controlled relative to the body of gas into which they are sprayed. This can be achieved by controlling the droplets' initial velocity and/or the velocity of the body of gas into which they are sprayed.

It is clearly desirable to be able to control the size of the droplet formed during the spray drying process and the droplet size will affect the size of the dried particle. Preferably, the droplet forming means also produces a relatively narrow droplet, and therefore particle, size distribution. This will lead to a dry powder formulation with a more uniform particle size and thus a more predictable and consistent FPF and FPD, by reducing the mass of particles with a size above a defined limit, preferably 90% below 5μm, below 3μm or below 2μm.

The ability to control the velocity of the droplet also allows further control over the properties of the resulting particles. In particular, the gas speed around the droplet

will affect the speed with which the droplet dries. In the case of droplets which are moving quickly, such as those formed using a 2-fluid nozzle arrangement (spraying into air), the air around the droplet is constantly being replaced. As the solvent evaporates from the droplet, the moisture enters the air around the droplet. If this moist air is constantly replaced by fresh, dry air, the rate of evaporation will be increased. In contrast, if the droplet is moving through the air slowly, the air around the droplet will not be replaced and the high humidity around the droplet will slow the rate of drying. As discussed below in greater detail, the rate at which a droplet dries affects various properties of the particles formed, including FPF and FPD.

Preferably, the velocity of droplets at 10mm from their point of generation is less than 100m/s, more preferably less than 50m/s, still more preferably less than 20m/s, most preferably less than 10m/s. Preferably the velocity of the gas, used in the generation of the droplets, at 10mm from the point at which they are generated is less than 100m/s, more preferably less than 50m/s, still more preferably less than 20m/s, most preferably less than 10m/s. In an embodiment, the velocity of the droplets relative to the body of gas into which they are sprayed, at 10mm from their point of generation, is less than 100m/s, more preferably less than 50m/s, still more preferably less than 20m/s, most preferably less than 10m/s.

Preferably, the velocity of droplets at 5mm from their point of generation is less than 100m/s, more preferably less than 50m/s, still more preferably less than 20m/s, most preferably less than 10m/s. Preferably the velocity of the gas, used in the generation of the droplets, at 10mm from the point at which they are generated is less than 100m/s, more preferably less than 50m/s, still more preferably less than 20m/s, most preferably less than 10m/s. In an embodiment, the velocity of the droplets relative to the body of gas into which they are sprayed, at 10mm from their point of generation, is less than 100m/s, more preferably less than 50m/s, still more preferably less than 20m/s, most preferably less than 10m/s.

Preferably, the output per single piezo unit (for such a unit oscillating at > 1.5 MegaHz) is greater than 1.0cc/min, greater than 3.0cc/min, greater than 5.0cc/min,

greater than 8.0cc/min, greater than 10.0cc/min, greater than 15.0cc/min, or greater than 20.0cc/min. Such units should then produce dry particles with at least 90% by weight of the active particles in a dry powder formulation as measured by Malvern Mastersizer from a dry powder dispersion unit of less than 3μm, less than 2.5μm or less than 2μm.

Preferably, the output per single piezo unit (for such a unit oscillating at > 2.2 MegaHz) is greater than 0.5cc/min, greater than 1.0cc/min, greater than 3.0cc/min, greater than 5.0cc/min, greater than 8.0cc/min, greater than 10.0cc/min, greater than 15.0cc/min, or greater than 20.0cc/min. Such units should then produce dry particles with D(90) as measured by Malvern Mastersizer from a dry powder dispersion unit of less than 3μm, less than 2.5μm, or less than 2μm.

Preferably, the means for producing droplets moving at a controlled velocity and of a predetermined size is an alternative to the commonly used 2-fluid nozzle. In one embodiment, an ultrasonic nebuliser (USN) is used to form the droplets in the spray drying process.

Whilst ultrasonic nebulisers (USNs) are known, these are conventionally used in inhaler devices, for the direct inhalation of solutions containing drug, and they have not previously been widely used in a spray drying apparatus. It has been discovered that the use of such a nebuliser in spray drying has a number of important advantages and these have not previously been recognised. The preferred USNs control the velocity of the particles and therefore the rate at which the particles are dried, which in turn affects the shape and density of the resultant particles. The use of USNs also provides an opportunity to perform spray drying on a larger scale than is possible using conventional spray drying apparatus with conventional types of nozzles used to create the droplets, such as 2-fluid nozzles.

The preferable USNs use an ultrasonic transducer which is submerged in a liquid. The ultrasonic transducer (a piezoelectric crystal) vibrates at ultrasonic frequencies to produce the short wavelengths required for liquid atomisation. In one common form of USN, the base of the crystal is held such that the vibrations are transmitted

from its surface to the nebuliser liquid, either directly or via a coupling liquid, which is usually water. When the ultrasonic vibrations are sufficiently intense, a fountain of liquid is formed at the surface of the liquid in the nebuliser chamber. Large droplets are emitted from the apex and a "fog" of small droplets is emitted. A schematic diagram showing how a standard USN works is shown in Figure 3.

The attractive characteristics of USNs for producing fine particle dry powders include: low spray velocity; the small amount of carrier gas required to operate the nebulisers; the comparatively small droplet size and narrow droplet size distribution produced; the simple nature of the USNs (the absence of moving parts which can wear, contamination, etc.); the ability to accurately control the gas flow around the droplets, thereby controlling the rate of drying; and the high output rate which makes the production of dry powders using USNs commercially viable in a way that is difficult and expensive when using a conventional two-fluid nozzle arrangement. This is because scaling-up of conventional spray drying apparatus is difficult and the use of space is inefficient in conventional spray drying apparatus which means that large scale spray drying requires many apparatus and much floor space.

USNs do not separate the liquid into droplets by increasing the velocity of the liquid. Rather, the necessary energy is provided by the vibration caused by the ultrasonic nebuliser.

Furthermore, the USNs may be used to adjust the drying of the droplets and to control the expression of the force control agent on the surface of the resultant particles. Where the active agent itself can act as a force control agent, spray drying with a USN can further help to control the positioning of the hydrophobic moieties so that the effect of including a force control agent can be achieved even without including one.

Thus, as an alternative to the conventional Büchi two-fluid nozzle, an ultrasonic nebuliser may be used to generate droplets of active agent, which are then dried within the Büchi drying chamber. In one arrangement, the USN is placed in the feed solution comprising an active agent in a specially designed glass chamber which

allows introduction of the cloud of droplets generated by the USN directly into the heated drying chamber of the spray dryer.

The two-fluid nozzle is left in place to seal the hole in which it normally sits, but the compressed air was not turned on. The drying chamber is then heated up to 150°C inlet temperature, with 100% aspirator setting. Due to the negative pressure of the Büchi system, the nebulised cloud of droplets is easily drawn into the drying chamber, where the droplets are dried to form particles, which are subsequently classified by the cyclone, and collected in the collection jar. It is important that the level of feed solution in the chamber is regularly topped up to avoid over concentration of the feed solution as a result of continuous nebulisation.

Two theories have been developed which describe the mechanism of liquid disintegration and aerosol production in ultrasonic devices (Mercer 1981, 1968 and Sollner 1936). Lang (1962) observed that the mean droplet size generated from thin liquid layers was proportional to the capillary wavelength on the liquid surface. Using the experimentally determined factor of 0.34, the droplet diameter D is given by:

$$d_p = 0.34 \ (8\pi\gamma/pf^2)^{1/3}$$

p = solution density g cm^{-3} (water = 1)
γ = surface tension dyn cm^{-1} (water = 70)
f = frequency (MHz)

This means that for a frequency of 1.7 MHz the calculated droplet size is 2.9μm and for 2.4MHz the calculated droplet size is 2.3μm. Atomisers are also available with frequencies up to 4MHz with a calculated droplet size of 1.6μm.

Clearly, this allows the size of the droplets to be accurately and easily controlled, which in turn means that the active particle size can also be controlled (as the dried particle size will depend, to a great extent, on the size of the droplet). Further, the USN provides droplets which are smaller than can be practically produced at a comparative output by a conventional 2 fluid nozzle.

In an embodiment of the present invention, the method of preparing the active particles involves the use of an ultrasonic nebuliser. Preferably, the ultrasonic nebuliser is incorporated in a spray drier.

One type of ultrasonic nebuliser which may be used in the present invention is described in the European Patent Application No. 0931595A1. This patent application described ultrasonic nebulisers which work extremely well in putting the present invention into practice.

Despite the fact that the ultrasonic nebulisers disclosed in this document are not envisaged as being part of a spray drying apparatus, the nebulisers may be simply and easily incorporated into a spray drier to produce excellent spray dried particles as indicated above.

The nebulisers disclosed in EP 0931595 A1 are used as air humidifiers. However, the droplets produced are of an ideal size range with a small size distribution for use in a spray drying process. What is more, the nebulisers have a very high output rate of several litres of feed liquid per hour and up to of the order of 60 litres per hour in some of the devices produced and sold the companies Areco and Sonear. This is very high compared to the 2-fluid nozzles used in conventional spray drying apparatus and it allows the spray drying process to be carried out on a commercially viable scale.

Other suitable ultrasonic nebulisers are disclosed in US Patent No. 6,051,257 and in WO 01/49263.

A further advantage of the use of USNs to produce droplets in the spray drying process is that the particles which are produced are small, spherical in shape and are dense. These properties provide improved dosing. Furthermore, it is thought that the size and shape of the particles produced reduces the drug's device retention to very low levels.

In addition, the USNs can produce comparatively very small droplets relative to other known atomiser types and this, in turn, leads to the production of very small particles. The mean particles produced by USNs tend to be within the size range of 0.05 to 5μm, 0.05 to 3μm, or even 0.05 to 1μm. This compares very favourably with the particle sizes which tend to be obtained using conventional spray drying techniques and apparatus, or obtained by milling. Both of these latter methods produce particles with a minimum size of around 1μm. These advantages associated with the use of USNs are discussed in greater detail below.

Preferably, for delivery to the lower respiratory tract or deep lung, the MMAD of the USN active particles is not more than 10μm, and preferably not more than 5μm, more preferably not more than 3μm, not more than 2μm, and may be less than 1.5μm, or less than 1.0μm. Ideally, at least 90% by weight of the active particles in a dry powder formulation should have a diameter (equivalent sphere) of not more than 10μm, preferably not more than 5μm, more preferably not more than 5μm, not more than3μm or not more than 2μm.

A USN was used to prepare dry powders using a feed solution of an active agent (heparin) alone, and a blend of active agent with 1% to 5% and 10% w/w FCA (l-leucine). The ultrasonic nebuliser output rate was 130 ml/hr. The furnace temperature of the nebulised powders was set at 350°C. Figure 4 shows a schematic drawing of the ultrasonic set-up.

In order to test the processing of the powders, work was conducted using a Monohaler and a capsule filled with 20mg powder and fired into a rapid TSI in the manner explained previously. The study used a TSI flow rate of 60lpm with a cut-off of approximately 5μm.

Three measurements were made for each blend and the results are summarised below in Table 9, giving the average values of the three sets of results obtained.

Table 9: rapid TSI results using the dry powder produced using a USN with varying amounts of FCA

Formulation	FPF% (metered dose)	FPD (mg)
Heparin (0% leucine)	1.1	0.22
Heparin + leucine (1% w/w)	17.4	3.5
Heparin + leucine (2% w/w)	30.2	6.0
Heparin + leucine (3% w/w)	28.6	5.7
Heparin + leucine (4% w/w)	48.4	9.7
Heparin + leucine (5% w/w)	41.5	8.3
Heparin + leucine (10% w/w)	55.8	11.8

The rapid TSI results using the dry powder produced using the USN indicate a very low aerosolisation efficiency for pure heparin particles, but an improvement appeared in FPF with addition of l-leucine as a FCA.

The reason for the poor performance of the pure drug particles compared to those produced using the two-fluid nozzle arrangement is due to the size of the particles produced by these two different processes. The particles of pure drug generated using the USNs are extremely small (D(50) in the order of 1μm) compared to those prepared using the two-fluid nozzle arrangement (D(50) in the order of 2.5μm). Without a FCA, the smaller particles produced using the USN exhibit a worse FPF than the larger particles produced by the two-fluid nozzle.

The morphology of the particles was viewed using scanning electron micrographs (SEMs).

Figure 5A shows SEM micrographs of USN spray dried heparin alone, whilst Figure 5B shows SEM micrographs of USN spray dried heparin with 10% leucine.

As can be clearly seem from the SEMs, the shape of particles formed by co-spray drying an active agent and leucine using a USN differs to that of particles formed by co-spray drying heparin and leucine using a conventional 2-fluid nozzle spray drying technique.

The SEM micrographs of pure heparin generated using a USN show that the particles have a size of generally less than 2μm. The SEMs also show that these particles tend to form "hard" agglomerates of up to 200μm.

In contrast, the SEMs of nebulised heparin and leucine show that the primary particles produced are of the same size as the pure heparin particles. However, these particles are discrete and agglomerates are less evident and less compacted in nature.

What is more, the distinctive dimples or wrinkles observed on the surface of the particles prepared by co-spray drying heparin and leucine using a 2-fluid nozzle spray drier (Figures 2A-2D) are less evident when the particles are spray dried using a USN. Despite this, the co-spray dried particles formed using a USN still have an improved FPF and FPD over particles formed in the same way but without the FCA. In this case, this improvement is clearly not primarily due to the shape of the particles, nor is it due to any increase in density or rugosity.

It is believed that the leucine concentration at the surface of the solid particles is governed by several factors. These include the concentration of leucine in the solution which forms the droplets, the relative solubility of leucine compared to the active agent, the surface activity of leucine, the mass transport rate within the drying droplet and the speed at which the droplets dry. If drying is very rapid it is thought that the leucine content at the particle's surface will be lower than that for a slower drying rate. The leucine surface concentration is determined by the rate of leucine transport to the surface, and its precipitation rate, during the drying process.

As mentioned above, high gas flow speed rates around the droplets can accelerate drying and it is thought that, because the gas speed around droplets formed using a USN is low in comparison to that around droplets formed using conventional 2-fluid nozzles, droplets formed using a USN dry more slowly than those produced by using conventional 2-fluid nozzles. The leucine (or other FCA) concentration on the shell of droplets and dried particles produced using a USN can be higher as a result. It is considered that these effects reduce the rate of solvent evaporation from

the droplets and reduce "blowing" and, therefore, are responsible for the physically smaller and smoother primary particles that are observed (Kodas, T.T and Hampden Smith, M., 1999, Aerosol Processing of materials, 440). In this last regard, and as previously noted, droplets formed by the 2-fluid nozzle system have rapid air flow around them and they, therefore, dry very rapidly, and markedly exhibit the effects of blowing.

It is also speculated that the slower drying rate which is expected when the droplets are formed using USNs allows the FCA to migrate to the surface of the droplet during the drying process. This migration may be further assisted by the presence of a solvent which encourages the hydrophobic moieties of the FCA to become positioned on the surface of the droplet. An aqueous solvent is thought to be of assistance in this regard.

With the FCA being able migrate to the surface of the droplet so that it is present on the surface of the resultant particle, it is clear that a greater proportion of the FCA which is included in the droplet will actually have the force controlling effect (as the FCA must be present on the surface in order for it to have this effect). Therefore, it also follows that the use of USNs has the further advantage that it requires the addition of less FCA to produce the same force controlling effect in the resultant particles, compared to particles produced using conventional spray drying methods.

Thus, it will not be necessary to include amounts of up to 50% w/w of FCA in the feed solution, as suggested in the prior art discussed above. Rather, it has been found that excellent FPF values are achieved when no more than 20% w/w FCA is included. Preferably, no more than 10% w/w, no more than 8% w/w, no more than 5% w/w, no more than 4% w/w, no more than 2% w/w or no more than 1% w/w FCA is spray dried using a USN. The amount of FCA included may be as low as 0.1% w/w where the active agent is not able to act as an FCA itself.

Naturally, where the active agent itself has hydrophobic moieties which can be presented as a dominant composition on the particle surface, no FCA need be included.

The movement of the FCA during the drying step of the spray drying process will also be affected by the nature of the solvent used in the host liquid. As discussed above, an aqueous solvent is thought to assist the migration of the hydrophobic moieties to the surface of the droplet and therefore the surface of the resultant particle, so that the force controlling properties of these moieties is maximised.

In a particle size study, the particle size of the spray dried particles formed using the USN was analysed. The dry powders were dispersed at 4bar in Sympatec particle sizer (Helos dry dispersed). The values of D10, D50 and D90 of the ultrasonic nebulised powders were measured and are indicated in Table 10 (10% by volume of the particles are of a size, measured by Sympatec, that is below the D10 value. 50% by volume of the particles are of a size, measured by Sympatec, that is below the D50 value and so on). The values are an average of three measurements.

In addition, the percentage mass of particles with a size of less than 5μm was obtained from the particle size data and is expressed as FPF.

Table 10: Particle size study of spray dried particles using USN, without secondary drying

Formulation	D10 (μm)	D50 (μm)	D90 (μm)	FPF% (<5μm)
Heparin (0% leucine)	0.43	1.07	4.08	90.52
Heparin + leucine (1% w/w)	0.41	0.90	1.79	99.97
Heparin + leucine (2% w/w)	0.41	0.89	1.75	100
Heparin + leucine (3% w/w)	0.41	0.88	1.71	100
Heparin + leucine (4% w/w)	0.41	0.86	1.71	100
Heparin + leucine (5% w/w)	0.41	0.90	1.84	100
Heparin + leucine (10% w/w)	0.41	0.89	1.76	100

Figure 6 shows a typical size distribution curve of three repeated tests of pure heparin powder generated using an ultrasonic nebuliser. The main peak represents the size of the individual active particles, ranging between 0.2μm and 4.5μm in diameter. The second, smaller peak between diameters of 17 to 35μm represents agglomerates of active particles.

Sympatec particle sizing (Helos dry dispersed) results showed that ultrasonic nebulised powders have a narrower size distribution and smaller mean particle size than the 2-fluid nozzle spray dried powders.

Figure 7A shows a comparison between particle size distribution curves of 2-fluid nozzle spray dried powders and ultrasonic nebulised powders comprising a blend of heparin with 2% leucine w/w.

Figure 7B shows a comparison between particle size distribution curves of 2-fluid nozzle spray dried powders and ultrasonic nebulised powders comprising a blend of heparin with 5% leucine w/w.

Figure 7C shows a comparison between particle size distribution curves of 2-fluid nozzle spray dried powders and ultrasonic nebulised powders comprising a blend of heparin with 10% leucine w/w.

These figures show a gradual disappearance of the second peak, indicating that the incidence of agglomerates is reduced as the amount of co-spray dried FCA is increased.

For the USN, spray dried material, agglomerate peaks disappears under the same test conditions when >3% leucine is added. For the 2-fluid nozzle spray dried material, agglomerate peaks disappear under the same test conditions when >10% leucine is added. This indicates that adding leucine as an FCA reduces the strength of the agglomerates in heparin powder. It further suggests that ultrasonic nebulised materials de-agglomerate more easily at lower leucine (FCA) contents. This may be related to the surface concentration of the leucine (FCA), as mentioned above.

The SEM images of ultrasonic nebulised powders (Figures 5A and 5B) also support the finding that addition of leucine facilitates aerosolisation. SEMs of pure heparin showed that although heparin primary particles are generally <2μm, large distinct agglomerates are formed. The SEMs of all of the powders comprising heparin and leucine show that the primary particle size is still <2μm, but the large hard agglomerates are not evident.

It can be seen that particles formed using a spray drying process involving an ultrasonic nebuliser have been found to have a greater FPF than those produced using a standard spray drying apparatus, for example with a two fluid nozzle configuration.

What is more, the particles formed using a spray drying process using a USN have been found to have a narrower particle size distribution than those produced using a standard spray drying apparatus, for example with a two fluid nozzle configuration.

Studies of the particles produced by spray drying using USNs have led to the discovery that the bulk density of ultra-fine drug powders can be beneficially increased whilst also improving aerosolisation characteristics. This finding is contrary to conventional thinking and in marked contrast to the prior art approaches to improving aerosolisation, whereby drug particles and formulations are prepared having reduced density. Whilst low density particles can improve aerosolisation, they place significant limitations on payload mass which can be delivered as a single inhalation. For example, a size 3 capsule (the type of capsule used in Cyclohaler (trade mark), Rotahaler (trade mark) and many other capsule-based DPIs) which conventionally holds 20mg of formulated powder might only accommodate 5mg or less of low density material.

The significance and commercial benefit of high density or densified powder particles is that it provides the potential to deliver increased powder payloads in smaller volumes. For example, a size 3 capsule which conventionally holds a 20mg payload, may be able to accommodate up to 40mg of a higher density powder

formulation and an Aspirair (trade mark) blister designed to hold a 5mg payload may be used to hold 15mg of a higher density powder such as that which may be produced using the present invention. This is particularly important for drugs requiring high dose delivery, including, for example, heparin, where doses in the region of 40-50mg may be required. It should be possible to incorporate this dose in the form of a high density powder into a blister or capsule which holds just 20-25mg of a standard density powder.

Using the above described spray drying process using a USN, the final density of particles comprising active agent and FCA (heparin and leucine) has been increased by controlled atomisation and drying. The ability to increase density, as noted above, provides an opportunity to increase drug payloads filled into a unit blister or capsule whilst, in this case, raising FPD from 20% for conventionally spray dried heparin to 70% for heparin and an FCA spray dried according to the present invention.

The key to improved aerosolisation in a denser particle is the presence of FCA, without which the benefits of densification cannot be realised. The process by which densification is brought about is also critical in terms of the spatial positioning of the FCA on the drug particle surface. The aim is always to provide the maximum possible surface presence of FCA in the densified drug composite. In the case of the spray drying according to the present invention, conditions are selected to provide FCA surface enrichment of resultant drug particles.

Similar results to those shown above when using USNs are expected for spray drying using other means which produce low velocity droplets at high output rates. For example, further alternative nozzles may be used, such as electrospray nozzles or vibrating orifice nozzles. These nozzles, like the ultrasonic nozzles, are momentum free, resulting in a spray which can be easily directed by a carrier air stream, however, their output rate is generally lower.

Another attractive type of nozzle for use in a spray drying process is one which utilises electro-hydrodynamic atomisation. A tailor cone is created at a fine needle

by applying high voltage at the tip. This shatters the droplets into an acceptable monodispersion. This method does not use a gas flow, except to transport the droplets after drying. An acceptable monodispersion can also be obtained utilising a spinning disc generator.

The nozzles such as ultrasonic nozzles, electrospray nozzles or vibrating orifice nozzles can be arranged in a multi nozzle array, in which many single nozzle orifices are arranged in a small area and facilitate a high total throughput of feed solution. The ultrasonic nozzle is an ultrasonic transducer (a piezoelectric crystal). If the ultrasonic transducer is located in an elongate vessel the output may be raised significantly.

Moisture Profiling

The spray drying process may include a further step wherein the moisture content of the spray dried particles is adjusted to allow fine-tuning of some of the properties of the particles.

When active particles are produced by spray drying, some moisture will remain in the particles. This is especially the case where the active agent is temperature sensitive and does not tolerate high temperatures for the extended period of time which would normally be required to remove further moisture from the particles.

The amount of moisture in the particles will affect various particle characteristics, such as density, porosity, flight characteristics, and the like.

Therefore, according to a further aspect of the present invention, a method of preparing a dry powder composition is provided, wherein the method comprises a step of adjusting the moisture content of the particles.

In one embodiment, the moisture adjustment or profiling step involves the removal of moisture. Such a secondary drying step preferably involves freeze-drying, wherein the additional moisture is removed by sublimation. An alternative type of drying for this purpose is vacuum drying.

Generally, the secondary drying takes place after the active has been co-spray dried with a force control agent. In another embodiment, the secondary drying takes place after nebulised active agent has been spray dried, wherein the active agent was optionally in a blend with a FCA.

The secondary drying step has two particular advantages. Firstly, it can be selected so as to avoid exposing the pharmaceutically active agent to high temperatures for prolonged periods. Furthermore, removal of the residual moisture by secondary drying is significantly cheaper than removing all of the moisture from the particle by spray drying. Thus, a combination of spray drying and freeze-drying or vacuum drying is economical and efficient, and is suitable for temperature sensitive pharmaceutically active agents.

In order to establish the effect of secondary drying of the powders, samples of active agent alone and of a combination of active agent (heparin) and an FCA (leucine 10% w/w), were secondary dried at 50°C under vacuum for 24 hours.

The results set out in Table 11 indicate the secondary drying step further raised the FPF and FPD, when they are compared to the results in Table 10, which relates to equivalent particles which have not undergone secondary drying.

Table 11: rapid TSI results using the dry powder produced using a USN with varying amounts of FCA, after secondary drying

Formulation	FPF% (metered dose)	FPD (mg)
Heparin (0% leucine)	4.1	0.82
Heparin + leucine (10% w/w)	70.8	14.2

In a later stage experiments have been conducted on samples of active agent (heparin) and an FCA (leucine 5% w/w), were secondary dried at 40°C under vacuum for 24 hours.

Particle size tests were also conducted to show the effect of secondary drying. The particle size of the spray dried particles formed using the USN was analysed. The dry powders were dispersed at 4bar in a Helos disperser. The powders were secondary dried over 24 hours under vacuum.

The values of FPF <5μm and D10, D50 and D90 of the ultrasonic nebulised powders were measured and are indicated in Table 12.

Table 12: Particle size study of spray dried particles using USN, after secondary drying

Formulation	D10	D50	D90	FPF% (<5μm)
Heparin (0% leucine)	0.44	1.06	2.93	92.35
Heparin + leucine (10% w/w)	0.40	0.87	1.77	100

Thus, by comparing the results in Table 12 with those of Table 10, one can see that secondary drying particles did not result in any significant change in particle size, both for active agent alone and for a blend of active agent and FCA.

Figure 6 shows a comparison between particle size distribution curves of secondary dried and not secondary dried powders. The powder used was heparin with 10% leucine w/w. Clearly, there is virtually no difference between the curves, illustrating that secondary drying does not have an effect on particle size.

Then, in order to establish whether the effect of secondary drying varied between particles produced using a USN and a 2-fluid nozzle, the particle size study of secondary drying with spray dried particles formed using the USN was repeated but using a 2-fluid nozzle spray drier. Once again, the powders were secondary dried over 24 hours under vacuum. Values of FPF <5μm and D10, D50 and D90 of the spray dried powders are indicated in 13 below.

Table 13: Particle size study of 2-fluid nozzle spray dried particles after secondary drying

Formulation	D10	D50	D90	FPF% (<5μm)
Heparin + leucine (2% w/w)	0.59	2.09	5.19	89.57
Heparin + leucine (5% w/w)	0.61	2.16	4.77	91.18

Heparin + leucine (10% w/w)	0.58	2.04	3.93	96.6
Heparin + leucine (25% w/w)	0.63	2.34	4.85	91.15
Heparin + leucine (50% w/w)	1.05	3.03	6.62	80.03

Figures 2E to 2H show SEM micrographs of 2-fluid nozzle spray dried heparin with 2, 5, 10 and 50% leucine, after secondary drying. When one compares the particles in these Figures to those in Figures 2A to 2D, it can be seen that the secondary drying does appear to increase the "collapse" of the particles. Thus, even at low percentages of FCA, the secondary dried particles have a more wrinkled or shrivelled shape.

Table 14: Moisture content of 2 fluid nozzle spray dried particles under standard condition

Formulation	**% w/w Moisture before secondary drying**	**% w/w Moisture after secondary drying**
Heparin + Leucine 5%	9.57	2.18

The above discussed experiments and the moisture content values determined by Karl-Fisher methodology set out in Table 14 show that secondary drying significantly reduces the moisture content of heparin particles (by approximately 6.5 %). This would imply that the heparin is drying in such a way that there is a hard outer shell holding residual moisture, which is driven off by secondary drying, and entrapped moisture is trapped with in a central core. One could infer that the residence time of the particle in the drying chamber is too short, and that the outer shell is being formed rapidly and is too hard to permit moisture to readily escape during the initial spray drying process.

Secondary drying can also be beneficial to the stability of the product, by bringing down the moisture content of a powder. It also means that drugs which may be very heat sensitive can be spray dried at lower temperatures to protect them, and then subjected to secondary drying to reduce the moisture further, and protect the drug. In another embodiment of the third aspect of the invention, the moisture profiling involves increasing the moisture content of the spray dried particles.

In another embodiment of the third aspect of the invention, the moisture profiling involves increasing the moisture content of the spray dried particles.

Preferably, the moisture is added by exposing the particles to a humid atmosphere. The amount of moisture added can be controlled by varying the humidity and/or the length of time for which the particles are exposed to this humidity.

Ultrasonic nebulised formulations comprising clomipramine and heparin were prepared next and were tested in Aspirair (trade mark) and MonoHaler (trade mark) devices.

The heparin formulation was produced from the original powder, using a spray drying system according to the present invention, as described above. This system comprises an ultrasonic nebulisation unit, a gas flow for transporting the droplets nebulised into a heated tube to dry the droplets, and a filtration unit for collecting the dried particles.

An aqueous solution of the heparin was made containing 1% w/w relative to the water. Leucine, a force control agent, was added to this in an amount sufficient to make 5% w/w relative to the heparin.

The solution was nebulised with a frequency of 2.4MHz and guided through the tube furnace with furnace surface temperature heated to approximately 300°C, after which the dried powder was collected. The gas temperature was not measured, but was substantially less than this temperature. Malvern Mastersizer (dry powder) particle size measurement gave a d(50) of 0.8μm.

The clomipramine hydrochloride formulation was produced from the original powder, using the same spray drying system as noted above for heparin. This system comprises an ultrasonic nebulisation unit, a gas flow for transporting the droplets nebulised into a heated tube to dry the droplets, and a filtration unit for collecting the dried particles.

An aqueous solution of the clomipramine hydrochloride was made containing 2% w/w relative to the water. Sufficient leucine was added to make 5% w/w relative to the drug.

The solution was nebulised with a frequency of 2.4MHz and guided through the tube furnace with furnace surface temperature heated to approximately 300°C, after which the dried powder was collected. The gas temperature was not measured, but was substantially less than this temperature. Malvern (dry powder) particle size measurement gave a d(50) of 1.1μm

The Malvern particle size distributions show that both the heparin and the clomipramine hydrochloride have very small particle sizes and distributions. The d(50) values are 0.8μm for heparin and 1.1μm for clomipramine hydrochloride. The modes of the distribution graph are correspondingly 0.75 and 1.15. Further, the spread of the distributions is relatively narrow, with d(90) values of 2.0μm and 2.5μm respectively, which indicates that substantially all of the powder by mass is less than 3μm and, in the case of the heparin, less than 2μm. Heparin shows a smaller particle size and size distribution than clomipramine hydrochloride, probably due to lower concentration in solution.

Approximately 3mg and 5mg of the heparin formulation and 2mg of the clomipramine hydrochloride formulation were then loaded and sealed into foil blisters. These were then fired from an Aspirair device into a Next Generation Impactor (NGI) with air flow set at 90l/min. The results for the heparin are based upon a cumulative of 5 fired blisters. Only 1 blister shot was fired for each clomipramine hydrochloride NGI.

Approximately 20mg of the heparin or the clomipramine hydrochloride formulations were loaded and sealed into size 3 capsules. The clomipramine hydrochloride capsules were gelatine capsules and the capsules used for the heparin formulation were HPMC capsules (hydroxypropylmethyl cellulose). These capsules were then fired using the MonoHaler device into a NGI with an air flow set at 90l/min.

The performance data are summarised as follows, the data being an average of 2 or 3 determinations:

Table 15: Powder performance study of drug and 5% leucine dispensed using Aspirair (trade mark)

Aspirair	MD (μm)	DD (μm)	FPD (μm)	FPF% (<5μm)	FPF% (<3μm)	FPF% (<2μm)	FPF% (<1μm)
Heparin 3mg	1969	1870	1718	92	83	69	39
Heparin 5mg	3560	3398	3032	89	78	60	31
Clomipramine 2mg	1739	1602	1461	91	81	62	28

Table 16: Powder performance study of drug and 5% leucine dispensed using Aspirair (trade mark)

Aspirair	MMAD	Throat (%)	Blister (%)	Device (%)
Heparin 3mg	1.30	5	2	2
Heparin 5mg	1.57	6	2	2
Clomipramine 2mg	1.56	4	3	5

Table 17: Powder performance study of drug and 5% leucine dispensed using Monohaler (trade mark)

Monohaler	MD (μm)	DD (μm)	FPD (μm)	FPF% (<5μm)	FPF% (<3μm)	FPF% (<2μm)	FPF% (<1μm)
Heparin 20mg	14201	12692	10597	83	70	54	29
Clomipramine 20mg	18359	16441	12685	77	56	37	19

Table 18: Powder performance study of drug and 5% leucine dispensed using Monohaler (trade mark)

Monohaler	MMAD	Throat (%)	Blister (%)	Device (%)
Heparin 20mg	1.72	6	5	6
Clomipramine 20mg	2.38	10	1	9

The device retention in the Aspirair device was surprisingly low (between 2-5%) for both drug formulations. This was especially low given the small particle sizes used and the relatively high dose loadings used: for example the clomipramine hydrochloride exhibited device retention in the Aspirair device of 5% and a small d(50) of 1.1μm. In comparison, clomipramine hydrochloride co-jet milled with 5% leucine with a d(50) of 0.95μm gave a device retention of 23% under otherwise similar circumstances. Heparin gave very low device retention in Aspirair with a d(50) of 0.8μm and there did not appear to be a difference in device retention using the 3mg or 5mg filled blisters.

When using the Monohaler device to dispense the formulations, the device retention was higher than observed when the Aspirair device was used. However, device retention of respectively 6% for heparin and 9% for clomipramine hydrochloride still appears to be relative low for a formulation that comprises >90% ultrafine drug.

Throat retention was also very low for both drug formulations. When the formulations were dispensed using the Aspirair, it was as low as 4%. With Monohaler as the device, the results show slightly higher throat retention (between 6-10%).

It has previous been argued that as particle size was reduced, powder surface free energy and hence powder adhesivity and cohesivity would increase. This would be expected to result in increased device retention and poor dispersion. Such adhesivity and cohesivity and hence device retention/poor performance has been shown to be reduced by addition of force control agents, attached to the drug particle surface (or drug and excipients as appropriate). In Aspirair, it is believed that a level of adhesivity and cohesivity is desirable to prolong lifetime in the vortex, yielding a slower plume, but adhesivity and cohesivity should not be so high as to result in high device retention. Consequently a balance of particle size, adhesivity and cohesivity is believed to be required to achieve an optimum performance in Aspirair.

The dispersion results for both powders were also excellent when using Monohaler as the device.

It is believed that the results indicate that the ultrasonic nebulising process results in a most effective relative enrichment of leucine concentration at the particle surface. The surface enrichment is dependent upon the rate of leucine transport to the surface, the size of the particle, and its precipitation rate, during the drying process. This precipitation rate is related to the slow drying of the particles in this process. The resulting effect is that the particle surface is dominated by the hydrophobic aspects of the leucine. This presents a relatively low surface energy of the powder despite its small particle size and high surface area. It therefore appears that the addition of a force control agent is having a superior influence to adhesivity and cohesivity and hence the device retention and dispersion.

The inclusion of leucine appears to provide significant improvements to the aerosolisation of heparin and clomipramine hydrochloride, and should make both drugs suitable for use in a high-dose passive or active device.

From the results presented herein, it can be seen that improvement in the FPF of spray dried or nebulized active agents can be achieved by using one or more of the following:

1) tailored co-spray drying the active agent with a force control agent;
2) using a means of producing droplets for spray drying which results in slow velocity droplets, the size of which can be accurately controlled; and
3) moisture profiling of the spray dried particles.

The above discussion and experiments focussed on conventional spray drying apparatus and ultrasonic nebulizing apparatus. However, it should be noted that further changes to the apparatus may be made to ensure that the particles collected at the end of the spray drying process have the optimum properties.

For example, the nature of the drying chamber may be changed, to get better drying and/or other advantages. Thus, in one embodiment of the invention, a spray drying apparatus comprising a drying chamber with heated walls may be used. Such drying chambers are known and they have the advantage that the hot walls discourage deposition of the spray dried material on them. However, the heated walls create a temperature gradient within the drying chamber, where the air in the outer area of the chamber is hotter than that in the centre of the chamber. This uneven temperature can cause problems because particles which pass through different parts of the drying chamber will have slightly different properties as they may well dry to differing extents.

In an alternative embodiment, the spray drying apparatus comprises a radiative heat source in the drying chamber. Such heat sources are not currently used in spray drying. This type of heat source has the advantage that it does not waste energy heating the air in the drying chamber. Rather, only the droplets/particles are heated as they pass through the chamber. This type of heating is more even, avoiding the temperature gradients mentioned above in connection with drying chambers with heated walls. This also allows the particles to dry from inside the droplets thus reducing or avoiding crust forming.

In yet another embodiment, the spray dried particles are collected using a upstream vertical drying column. These columns are already known in spray drying devices and they collect the spray dried particles by carrying the particles up a vertical column using an air flow, rather than simply relying on gravity to collect the particles in a collection chamber. The advantage of using such a vertical drying column to collect the spray dried particles is that it allows for aerodynamic classification of the particles. Fine particles tend to be carried well by the air flow, whilst larger particles are not. Therefore, the vertical drying column does not collect these larger particles.

The present invention can be carried out with any pharmaceutically active agent. The preferred active agents include:

1) steroid drugs such as, for example, alcometasone, beclomethasone, beclomethasone dipropionate, betamethasone, budesonide, clobetasol, deflazacort, diflucortolone, desoxymethasone, dexamethasone, fludrocortisone, flunisolide, fluocinolone, fluometholone, fluticasone, fluticasone proprionate, hydrocortisone, triamcinolone, nandrolone decanoate, neomycin sulphate, rimexolone, methylprednisolone and prednisolone;

2) antibiotic and antibacterial agents such as, for example, metronidazole, sulphadiazine, triclosan, neomycin, amoxicillin, amphotericin, clindamycin, aclarubicin, dactinomycin, nystatin, mupirocin and chlorhexidine;

3) systemically active drugs such as, for example, isosorbide dinitrate, isosorbide mononitrate, apomorphine and nicotine;

4) antihistamines such as, for example, azelastine, chlorpheniramine, astemizole, cetirizine, cinnarizine, desloratadine, loratadine, hydroxyzine, diphenhydramine, fexofenadine, ketotifen, promethazine, trimeprazine and terfenadine;

5) anti-inflammatory agents such as, for example, piroxicam, nedocromil, benzydamine, diclofenac sodium, ketoprofen, ibuprofen, heparinoid, nedocromil, cromoglycate, fasafungine and iodoxamide;

6) anticholinergic agents such as, for example, atropine, benzatropine, biperiden, cyclopentolate, oxybutinin, orphenadine hydrochloride, glycopyrronium, glycopyrrolate, procyclidine, propantheline, propiverine, tiotropium, tropicamide, trospium, ipratropium bromide and oxitroprium bromide;

7) anti-emetics such as, for example, bestahistine, dolasetron, nabilone, prochlorperazine, ondansetron, trifluoperazine, tropisetron, domperidone, hyoscine, cinnarizine, metoclopramide, cyclizine, dimenhydrinate and promethazine;

8) hormonal drugs such as, for example, protirelin, thyroxine, salcotonin, somatropin, tetracosactide, vasopressin or desmopressin;

9) bronchodilators, such as salbutamol, fenoterol and salmeterol;

10) sympathomimetic drugs, such as adrenaline, noradrenaline, dexamfetamine, dipirefin, dobutamine, dopexamine, phenylephrine, isoprenaline, dopamine, pseudoephedrine, tramazoline and xylometazoline;

11) anti-fungal drugs such as, for example, amphotericin, caspofungin, clotrimazole, econazole nitrate, fluconazole, ketoconazole, nystatin, itraconazole, terbinafine, voriconazole and miconazole;

12) local anaesthetics such as, for example, amethocaine, bupivacaine, hydrocortisone, methylprednisolone, prilocaine, proxymetacaine, ropivacaine, tyrothricin, benzocaine and lignocaine;

13) opiates, preferably for pain management, such as, for example, buprenorphine, dextromoramide, diamorphine, codeine phosphate, dextropropoxyphene, dihydrocodeine, papaveretum, pholcodeine, loperamide, fentanyl, methadone, morphine, oxycodone, phenazocine, pethidine and combinations thereof with an anti-emetic;

14) analgesics and drugs for treating migraine such as clonidine, codine, coproxamol, dextropropoxypene, ergotamine, sumatriptan, tramadol and non-steroidal anti-inflammatory drugs;

15) narcotic agonists and opiate antidotes such as naloxone, and pentazocine;

16) phosphodiesterase type 5 inhibitors, such as sildenafil; and

17) pharmaceutically acceptable salts of any of the foregoing.

A plurality of active agents can be employed in the practice of the present invention.

In preferred embodiments, the active agent is heparin, apomorphine, glycopyrrolate, clomipramine or clobozam.

In view of the increased FPF and FPD obtained, especially when co-spray drying an active agent with an FCA, it may be possible to do away with the large carrier particles in a dry powder comprising an active agent which has been co-spray dried with a force control agent. However, it may still be desirable to include carrier particles, especially where the active agent is to be administered in small amounts, as the bulk of the larger carrier particles will help to ensure that an accurate dose is dispensed.

Preferably, the active agent is a small molecule or the active agent is a carbohydrate, as opposed to a macromolecule. Preferably, the active agent is not a protein or polypeptide, and more preferably, the active agent is not insulin. In the case of proteins and in particular insulin, there is little or no benefit to be derived from the use of a force control agent in a dry powder formulation for administration by inhalation. The reason for this is that in the case of these active agents, the active agent itself acts as a force control agent and the cohesive forces of particles of these active agents are already only weak.

As discussed above, where the active agent being spray dried includes hydrophobic moieties itself, it is possible to spray dry the active agent without an FCA.

The active agent, preferably, exhibits greater than 20, 25, 30, and, more preferably, 40% bio-availability when administered via the lung in the absence of a penetration enhancer. Tests suitable for determining bio-availability are well known to those skilled in the art and an example is described in WO 95/00127. Agents that exhibit bio-availability of less than 20%, such as a majority of macromolecules, are insufficiently rapidly cleared from the deep lung and, as a result, accumulate to an unacceptable extent if administered to this location on a long term basis.

It is thought that the bio-availability of the active agent may be improved by delivering the active agent to the lung in particles with a size of less than 2μm, less than 1.5μm or less than 1μm. Thus, the spray dried particles of the present invention, which tend to have a particle size of between 0.5 and 5μm will exhibit excellent bio-availability compared to that of the particles produced by conventional spray drying processes.

In one embodiment of the present invention, the FCAs used are film-forming agents, fatty acids and their derivatives, lipids and lipid-like materials, and surfactants, especially solid surfactants.

Advantageously, the FCA includes one or more compounds selected from amino acids and derivatives thereof, and peptides and derivatives thereof. Amino acids, peptides and derivatives of peptides are physiologically acceptable and give acceptable release of the active particles on inhalation.

It is particularly advantageous for the FCA to comprise an amino acid. The FCA may comprise one or more of any of the following amino acids: leucine, isoleucine, lysine, cysteine, valine, methionine, and phenylalanine. The FCA may be a salt or a derivative of an amino acid, for example aspartame or acesulfame K. Preferably, the FCA consists substantially of an amino acid, more preferably of leucine, advantageously L-leucine. The D-and DL-forms may also be used. As indicated above, L-leucine has been found to give particularly efficient dispersal of the active particles on inhalation.

The FCA may comprise a metal stearate, or a derivative thereof, for example, sodium stearyl fumarate or sodium stearyl lactylate. Advantageously, the FCA comprises a metal stearate. For example, zinc stearate, magnesium stearate, calcium stearate, sodium stearate or lithium stearate.

The FCA may include or consist of one or more surface active materials, in particular materials that are surface active in the solid state. These may be water soluble or able to form a suspension in water, for example lecithin, in particular

soya lecithin, or substantially water insoluble, for example solid state fatty acids such as oleic acid, lauric acid, palmitic acid, stearic acid, erucic acid, behenic acid, or derivatives (such as esters and salts) thereof, such as glyceryl behenate. Specific examples of such materials are: phosphatidylcholines, phosphatidylethanolamines, phosphatidylglycerols, phosphatidylinositol and other examples of natural and synthetic lung surfactants; lauric acid and its salts, for example, sodium lauryl sulphate, magnesium lauryl sulphate; triglycerides such as Dynsan 118 and Cutina HR; and sugar esters in general. Alternatively, the FCA may be cholesterol or natural cell membrane materials, including pollen or spore cell wall components such as sporo-pollenins.

Other possible FCAs include sodium benzoate, hydrogenated oils which are solid at room temperature. In some embodiments, a plurality of different FCAs can be used.

Alternative FCAs which may be co-spray dried with the active agent include phospholipids and lecithins. However, where the active agent is insoluble in organic solvents, whilst the FCA is insoluble in an aqueous phase, or vice versa, in order to co-spray dry these incompatible materials, one must use a technique such as hydrophobic ion pairing or preferably co-solvents, i.e., a mixture of aqueous and organic solvents.

It is important to note that the particles produced by co-spray drying an active agent and an FCA will comprise both the active agent and the FCA and so the FCA will actually be administered to the lower respiratory tract or deep lung upon inhalation of the dry powder composition. This is in contrast to the additive material used in the prior art, which often was not administered to the deep lung, for example because it remains attached to the large carrier particles.

Thus, it is important that the selected FCA does not have a detrimental effect when administered to the lower respiratory tract or deep lung. Amino acids such as leucine, lysine and cysteine are all harmless in this regard, as are other FCAs such as phospholipids, when present in small quantities.

Claims

1. A method of making a dry powder composition for pulmonary inhalation, the method comprising spray drying a pharmaceutically active agent to produce active particles, wherein the active agent is spray dried using a spray drier comprising a means for producing droplets moving at a controlled velocity.

2. A method as claimed in claim 1, wherein the velocity of droplets at 5mm from their point of generation is less than 20m/s.

3. A method as claimed in claim 1 or 2, wherein the spray drier comprises an ultrasonic nebuliser.

4. A method as claimed in claim 3, wherein the output of each single nebuliser unit is greater than 5cc/min.

5. A method as claimed in claim 4, wherein the output of each single nebuliser unit is greater than 10cc/min.

6. A method as claimed in any one of the preceding claims, wherein 90% of the resulting dried particles have a size of less than 5μm, as measured by laser diffraction.

7. A method as claimed in claim 6, wherein 90% of the resulting dried particles have a size of less than 2.5μm, as measured by laser diffraction.

8. A method as claimed in any one of the preceding claims, wherein the resultant dried particles have a density greater than 0.1g/cc.

9. A method as claimed in any one of the preceding claims, wherein the active agent is co-spray dried with a force control agent.

10. A method as claimed in claim 9, wherein the force control agent is an amino acid, a phospholipid or a metal stearate.

11. A method as claimed in claim 10, wherein the force control agent is one or more of leucine, lysine and cysteine.

12. A method as claimed in any one of the preceding claims, wherein the active agent is a small molecule or carbohydrate.

13. A method as claimed in any one of the preceding claims, wherein the active agent is not a protein or polypeptide.

14. A method as claimed in any one of the preceding claims, wherein a blend of active agent and force control agent is spray dried, and the blend is a solution.

15. A method as claimed in any one of claims 1-13, wherein a blend of active agent and force control agent is spray dried, and the blend is a suspension.

16. A method as claimed in claim 14 or claim 15, wherein the active agent and force control agent are spray dried from an aqueous solution or suspension.

17. A method as claimed in any one of the preceding claims, wherein a solid content of up to 5% w/w active agent is spray dried.

18. A method as claimed in any one of the preceding claims, wherein the active agent is co-spray dried with a force control agent to produce dry particles comprising up to 50% w/w force control agent.

19. A method as claimed in claim 18, wherein the active agent is co-spray dried to produce dry particles comprising less than 10% w/w force control agent, less than 5% w/w, less than 3% w/w, less than 2% w/w or less than 1% w/w.

20. A method as claimed in claim 19, wherein the dry particles comprise less than 10% w/w amino acid.

21. A method as claimed in any one of the preceding claims, wherein the method comprises adjusting the moisture content of the spray dried particles.

22. A method as claimed in claim 21, wherein adjusting the moisture content involves a secondary drying step.

23. A method as claimed in claim 22, wherein the secondary drying step involves drying the spray dried particles under a vacuum or freeze-drying the particles.

24. A method as claimed in claim 21, wherein adjusting the moisture content involves increasing the moisture content of the particles.

25. A dry powder composition for pulmonary inhalation, wherein the composition comprises particles of pharmaceutically active material prepared using a method as claimed in any one of the preceding claims.

Abstract

Pharmaceutical Compositions

The present invention relates to improvements in dry powder formulations comprising a pharmaceutically active agent for administration by inhalation, and in particular to methods of preparing dry powder compositions with improved properties. In particular, spray drying processes are adapted and adjusted to obtain active particles with higher fine particle fractions and fine particle doses.

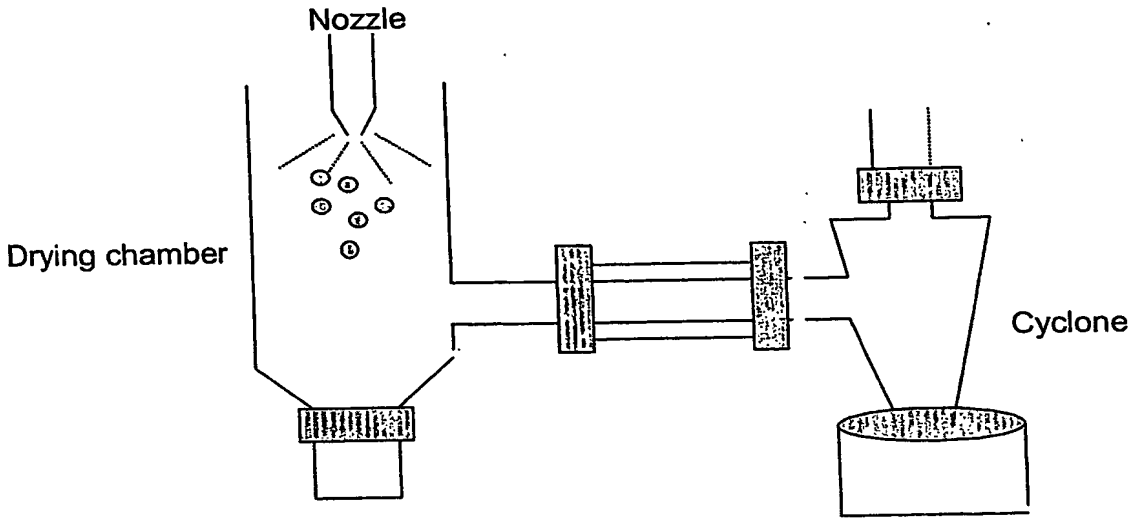


Figure 1

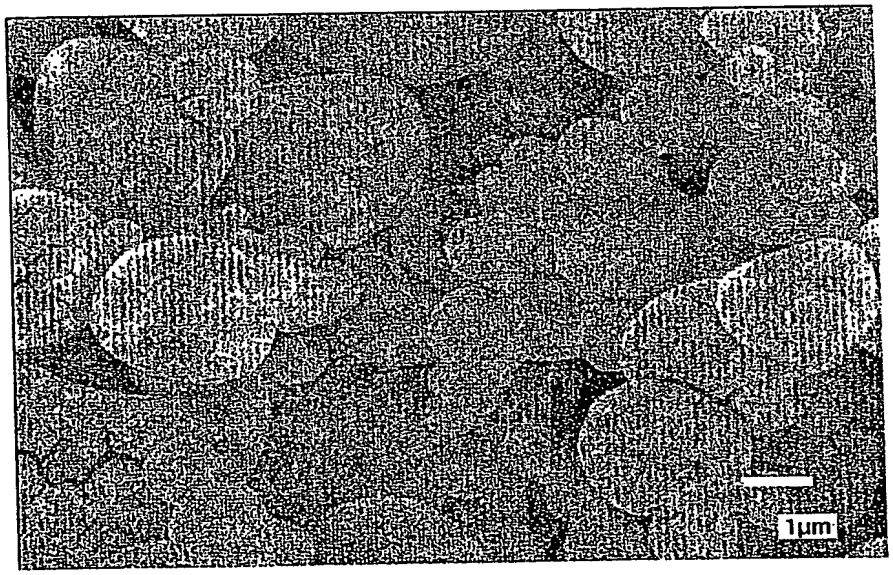


Figure 2a

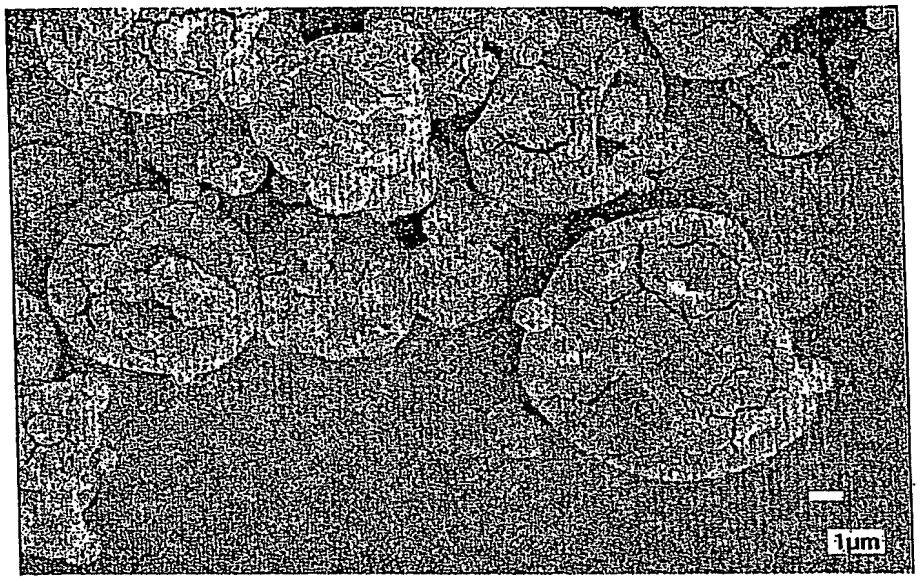


Figure 2b

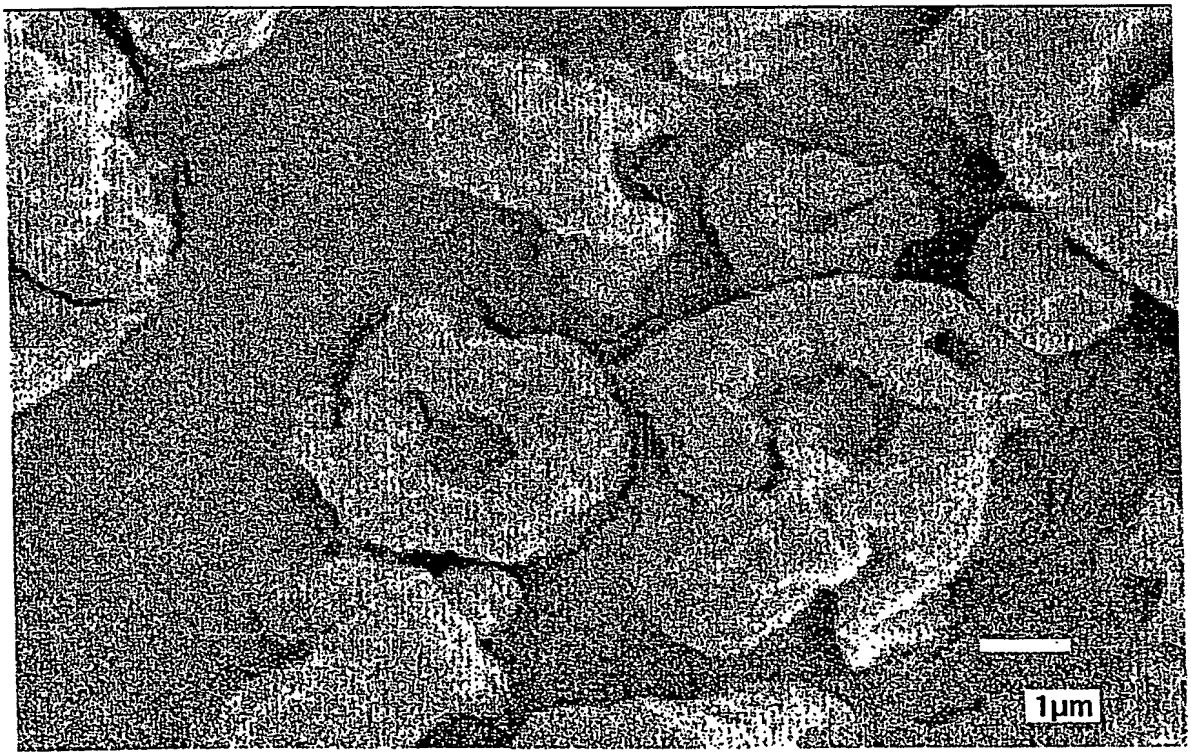
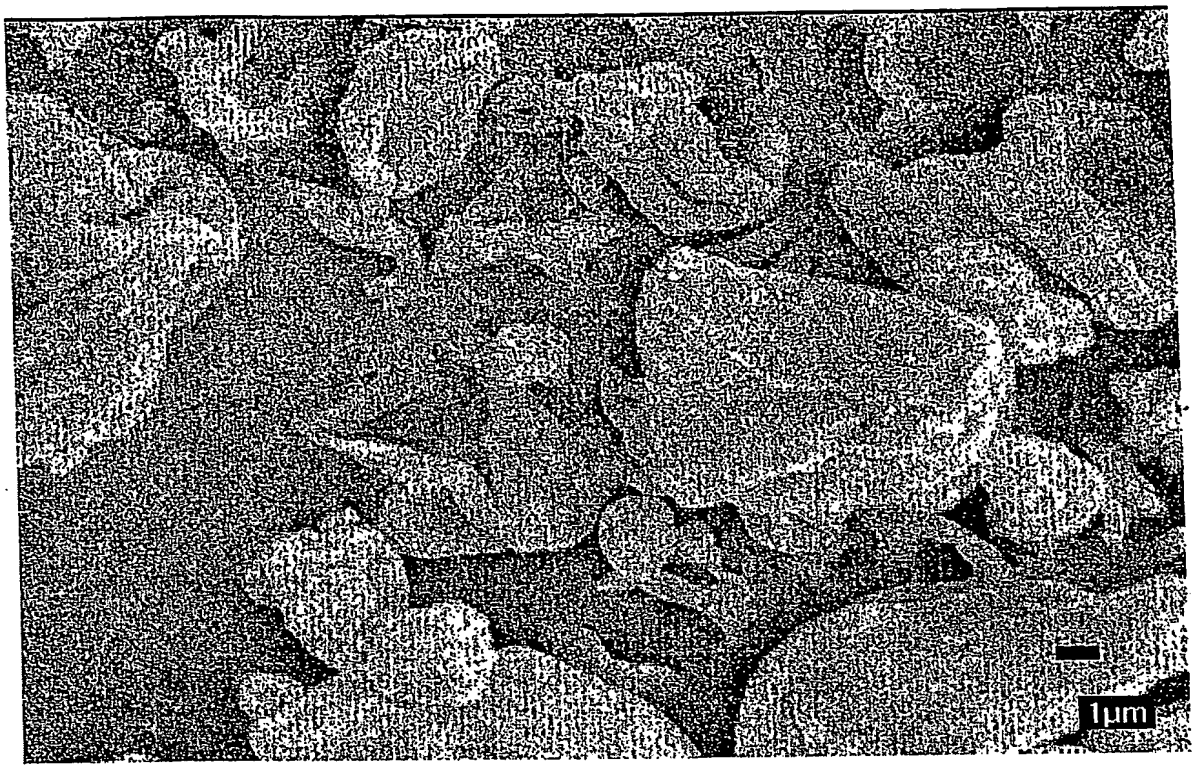


Figure 2c



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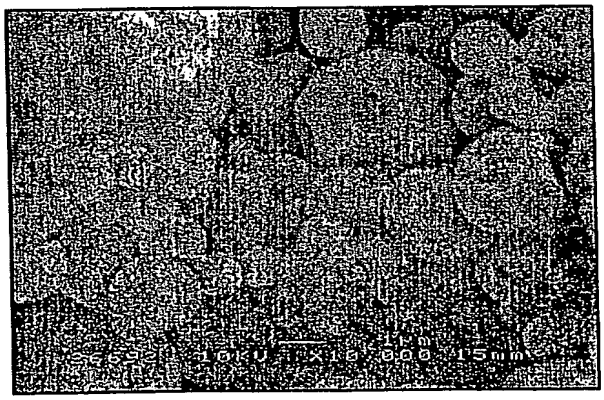

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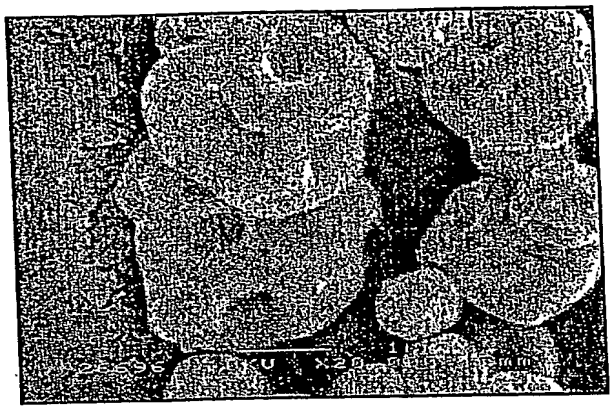

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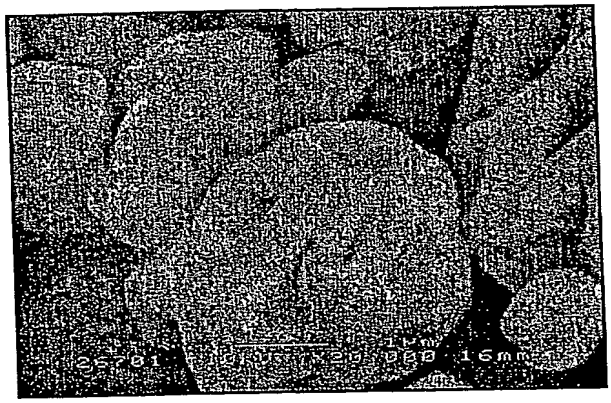
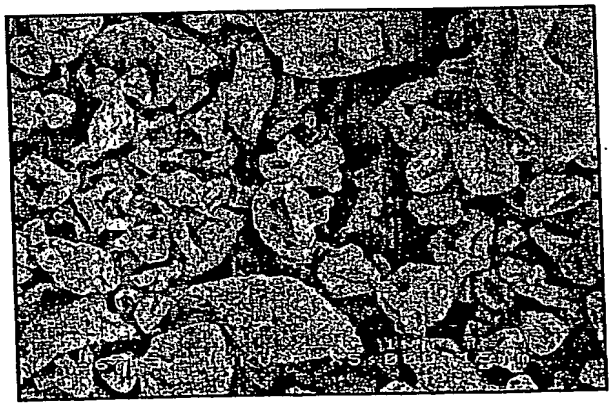


Figure 2g



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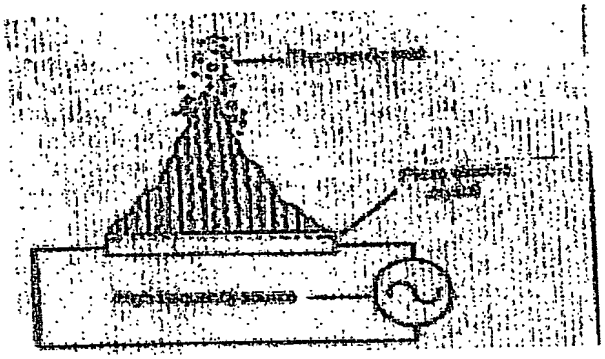

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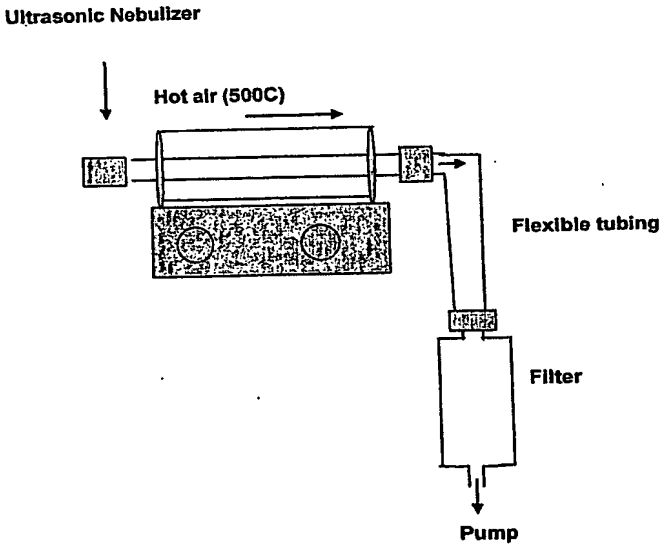


Figure 4

Figure 5a

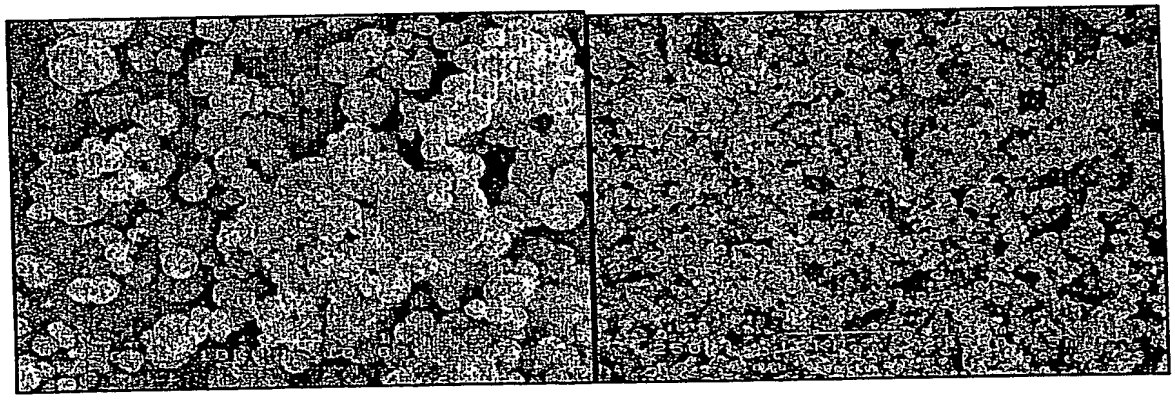
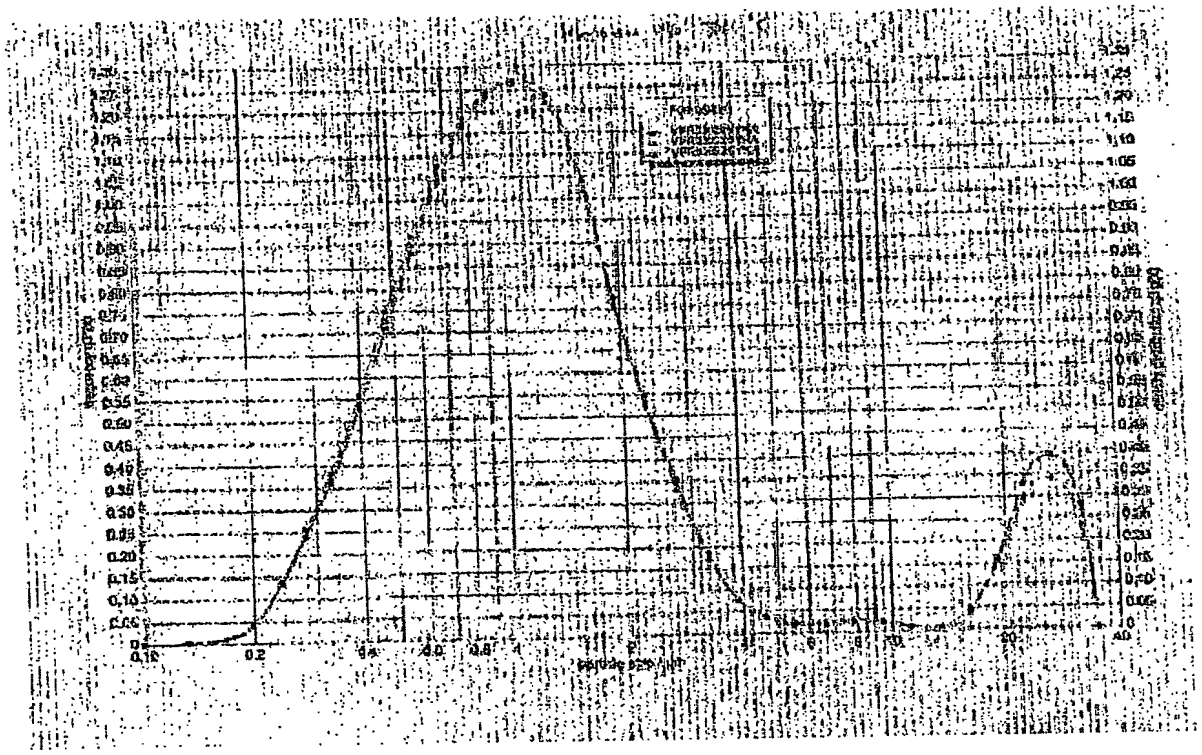


Figure 5b



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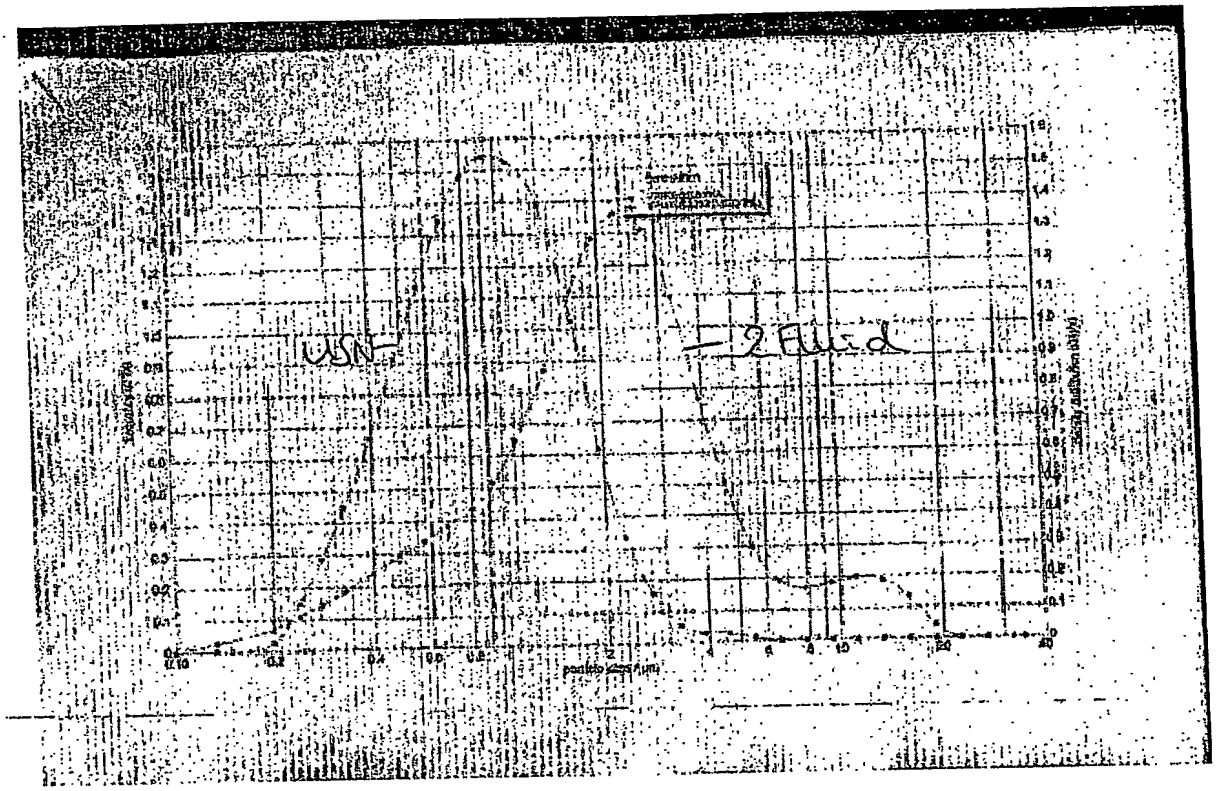

Figure 7a

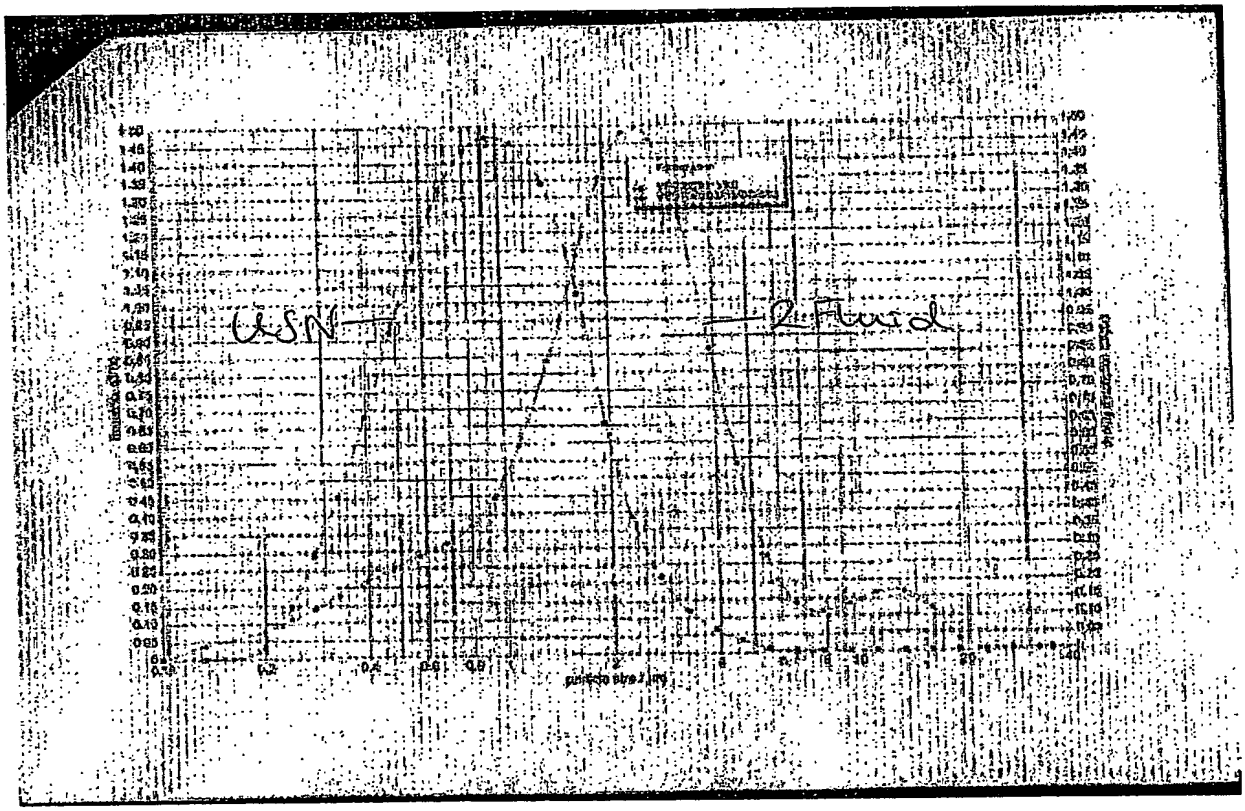

Figure 7b

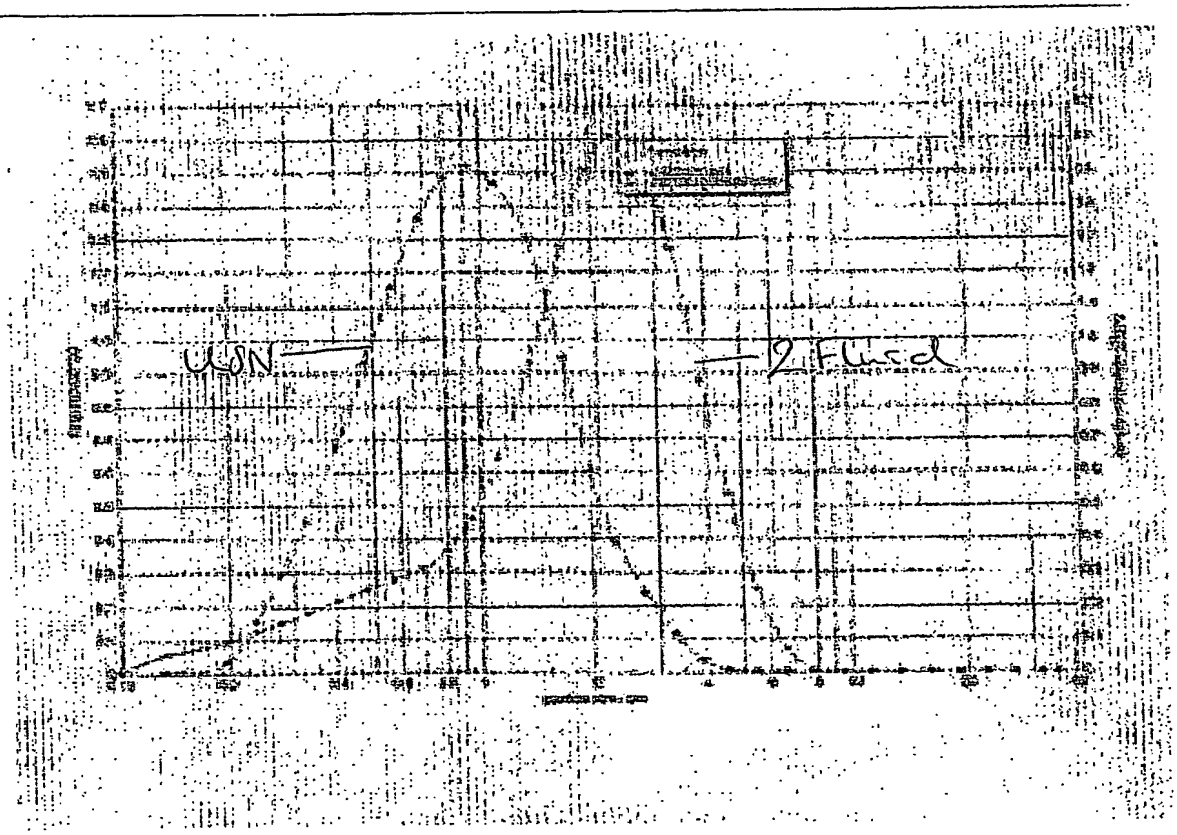

Figure 7c

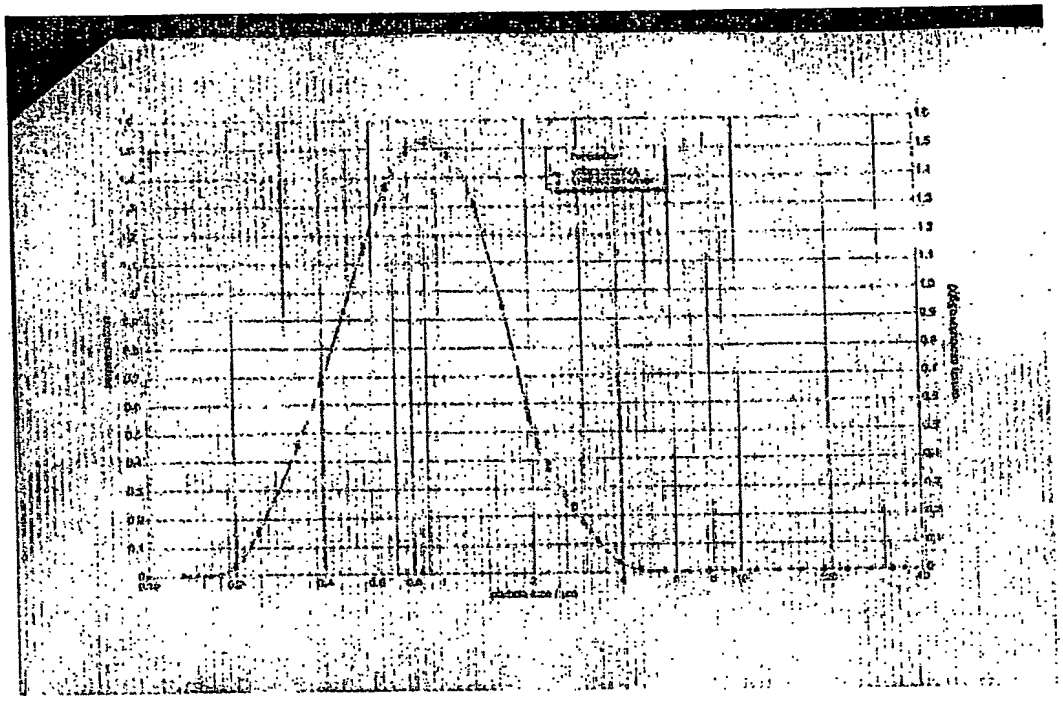

Figure 8